THERMAL AND PHOTOCHEMICAL DECOMPOSITION OF DIAZOALKENES AND RELATED DIAZAHETEROCYCLIC SYSTEMS

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by

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FOR MY PARENTS,

ANN KINNEAR AND ROBERT McEWAN

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A B S T R A C T

The work described in the first part of this Thesis concerns the thermal and photochemical decompositions of 1,2,3,3a-tetrahydro-10-phenylbenzo-[c]-cyclopenta-[f]-1,2-diazepine and 1,2,3,3a-tetrahydro-7-methyl-10-(p-tolyl)-benzo-[c]-cyclopenta-[f]-1,2-diazepine. At 400° in the gas phase, both benzodiazepines eliminate nitrogen, the product mixtures being 1,2,3,8-tetrahydro-8-phenyl-cyclopenta-[b]-indene, 1,2,3,3a-tetrahydro-8-phenylcyclopenta-[a]-indene and 9-cyclopent-1-enylfluorene, and 1,2,3,8-tetrahydro-5-methyl-8-(p-tolyl)cyclopenta-[b]-indene, 1,2,3,3a-tetrahydro-5-methyl-8-(p-tolyl)cyclopenta-[a]-indene and 3,6-dimethyl-9-cyclopent-1-enylfluorene respectively, formed *via* diradical intermediates.

Catalytic hydrogenation of these hydrocarbon mixtures afforded the simpler mixtures of 1-phenyl-1*H*-cyclopenta-[b]-indane and 9-cyclopentylfluorene and 1-(p-tolyl)-5-methyl-1*H*-cyclopenta-[b]-indane and 3,6-dimethyl-9-cyclopentylfluorene. 1,2,3,3a-Tetrahydro-7-fluoro-10-(p-fluoro)phenylbenzo-[c]-cyclopenta-[f]-1,2-diazepine reacted in a similar manner, giving analogous products.

At 260°, 1,2,3,3a-tetrahydro-10-phenylbenzo-[c]-cyclopenta-[f]-1,2-diazepine isomerised by an unprecedented ring-contraction of the azo-containing ring to give

3-/...

3-phenyl-3-cyclopent-1-enyl-3H-indazole. The mechanisms for these reactions have been investigated and overall reaction schemes are proposed.

In the solution phase, both benzodiazepines still eliminated nitrogen, but largely by a different mechanism from the gas phase case as evidenced by the different product distributions and the presence of the new major products 3-diphenylmethylenecyclopentene and 3-(di-p-tolyl)methylenecyclopentene respectively. Temperatures studied varied between 111° and 216°, and only at the higher temperatures was there any evidence for the fluorene products observed in the gas phase reactions. Concurrent with decomposition was the isomerisation to the indazole ring system as demonstrated by nmr spectroscopy and high speed liquid chromatography (HSLC). A double mechanism has been postulated for the decomposition in solution.

A study of the kinetics of the isomerisation of 1,2,3,3a-tetrahydro-10-phenylbenzo-[c]-cyclopenta-[f]-1,2-diazepine to 3-phenyl-3-cyclopent-1-enyl-3H-indazole has been initiated, with simultaneous development of the application of HSLC to kinetic analysis.

A preliminary study of the direct photolysis of the two benzodiazepines has also been made. Here, the hydrocarbon products were the same as those obtained in the gas phase at/...

at 400° although their ratios were different. The presence of the 3H-indazole early in the reaction was demonstrated by HSLC analysis.

In conclusion to Part I, a preliminary investigation of the photolysis of 2-diphenylmethylenecyclopentanone toluene-p-sulphonylhydrazone sodium salt has also been made. Here, the products obtained on hydrogenation were 1-phenyl-1H-cyclopenta-[b]-indane, (diphenylmethyl)cyclopentane and 1-phenyl-6,7-benzo-bicyclo-[3,2,1]-octan-8-one. The last-named was the major product isolated (69%).

The second part of this Thesis concerns the oxidation of γ,δ-unsaturated phenylhydrazones and methylhydrazones with activated manganese dioxide and lead tetraacetate in an attempt to obtain cyclised products. No cyclisations were observed, the main products being oxidative dimers or parent ketone in the MnO_2 reactions and the so-called azoacetates in the LTA reactions.

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PART I

THERMAL AND PHOTOCHEMICAL DECOMPOSITION OF DIAZOALKENES AND RELATED DIAZAHETEROCYCLIC SYSTEMS

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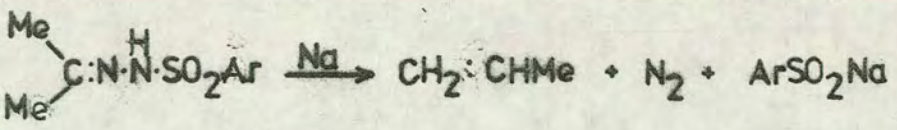
I N T R O D U C T I O N

A) GENERATION AND REACTIVITY OF DIAZOCOMPOUNDS FROM TOLUENE-p-SULPHONYLHYDRAZONE SALTS

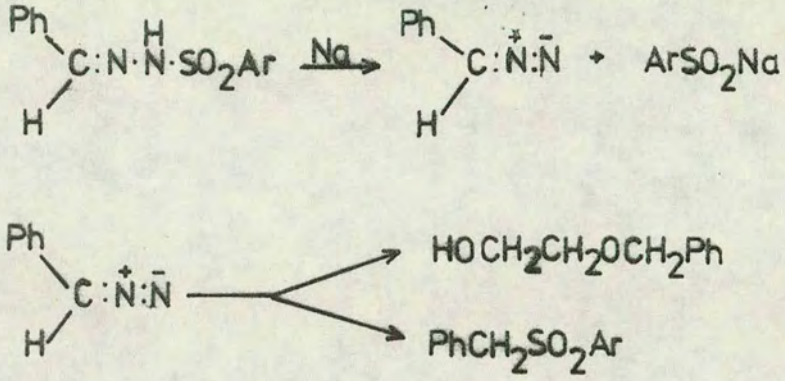
I BASE-INDUCED DECOMPOSITION OF TOLUENE-p-SULPHONYL HYDRAZONES

Since the initial observation in 1885 by Escales[1] that benzenesulphonylhydrazide was decomposed by warm alkali to give benzene, nitrogen and the benzenesulphinate anion, many groups of workers have shown interest in this type of reaction. Bamford and Stevens[2], for example, attempted unsuccessfully to obtain the olefin from the toluene-p-sulphonylhydrazone of the readily-enolisable ketone, ethyl acetoacetate. After this initial failure, the same workers investigated the decomposition of the toluene-p-sulphonylhydrazones of aliphatic ketones which were not readily enolised, and found that olefins were formed in good yield when the toluene-p-sulphonyl-hydrazones were heated in ethylene glycol with sodium:



In contrast to this, the toluene-p-sulphonylhydrazones of aromatic aldehydes and ketones afforded diazocompounds or/...

or products of their decomposition under similar conditions:

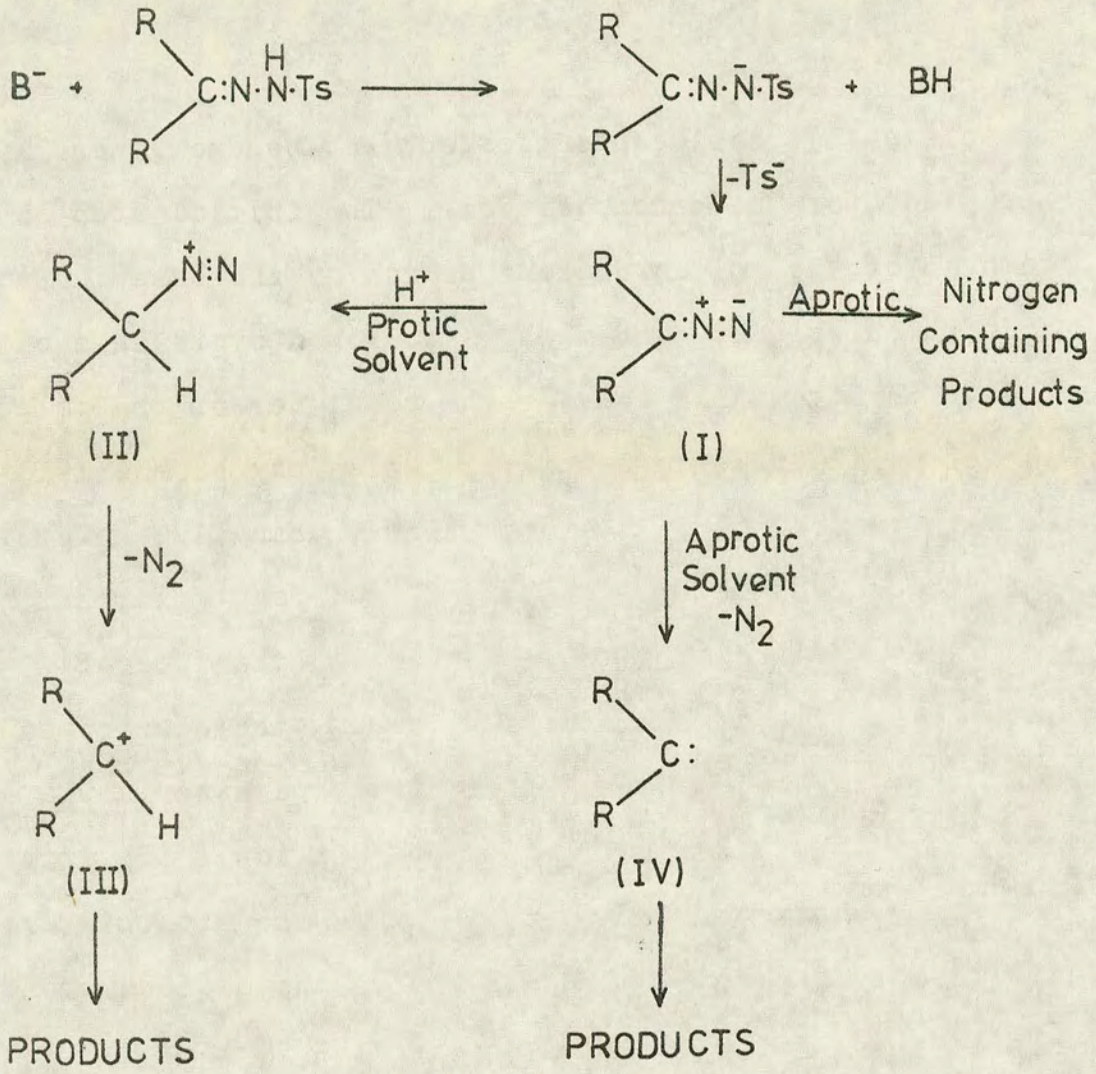


Subsequent work in this field has shown that toluene-p-sulphonylhydrazones can decompose with or without loss of nitrogen from the system thereby providing versatile synthetic routes to compounds as diverse as diazoalkanes, olefins, cyclopropanes and cyclopropenes, pyrazoles and other heterocyclic systems.

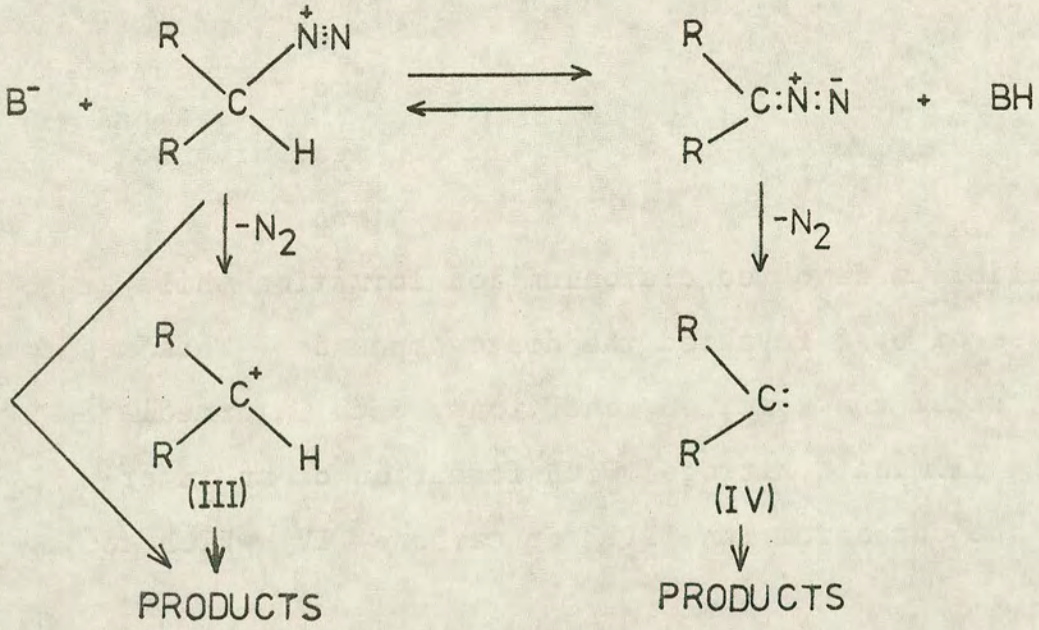
1) Formation of Diazocompounds

Because of the variety of products obtained, the mechanism of decomposition is of much interest, and investigations have shown that the mode of decomposition is both solvent- and base-dependent.

Through the work of Bamford and Stevens[2], Powell and Whiting[3], and Heubaum and Noyes[4], the mechanism, outlined in/...



Scheme (1)



Scheme (2)

in scheme (1), has been suggested, and become generally accepted, for the decomposition. The initial step is removal of the tosylhydrazone proton by the base (usually a sodium alkoxide), and this is followed by release of the sulphinate anion leaving the remainder of the molecule intact as the diazocompound (I), which may be the isolated product, depending on its stability. Usually, however, the diazocompound is not isolated, but reacts further, the mode of reaction being dependent on the type of solvent employed. In protic solvents, the diazocompound may be protonated, and the predominant pathway is *via* the diazonium cation (II) and carbonium ion (III) intermediates, whereas in aprotic solvents, the products are the result of direct decomposition of the diazocompound *i.e.* *via* the carbene (IV).

Shapiro and coworkers[5] studied the effect of base concentration on the decomposition, and found that this effect was as important to the mode of reaction as the nature of the solvent. These workers postulated an equilibrium between diazocompound and diazonium ion (scheme (2)). At low base concentration, this equilibrium favoured diazonium ion formation while an excess of base favoured the diazocompound. This meant that under the reaction conditions, both intermediates could eliminate nitrogen with formation of an intermediate carbonium ion (III) or carbene (IV) which could then/...

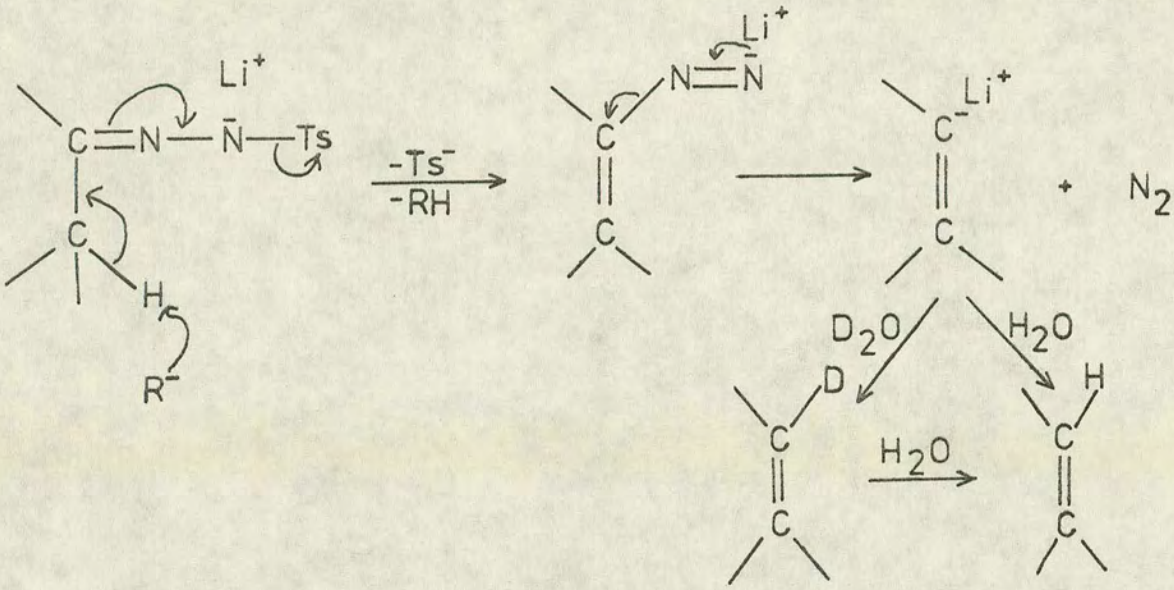
then react further to their respective products. (It is, however, possible for both intermediates to give the same products).

2) Photochemical Decomposition of Tosylhydrazone Salts

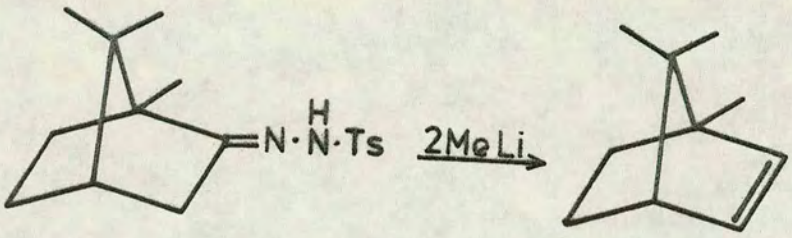
In 1962, Dauben and Wiley[6] reported the photochemical decomposition of the potassium salt of camphor toluene-p-sulphonylhydrazone. The products obtained were similar to the analogous thermal reaction. The same diazo-intermediate was proposed, and this was postulated to decompose further via the carbene route in aprotic solvents and by the diazonium cation and/or carbene species in protic solvents. A transient red colouration indicative of a diazocompound was observed during photolysis, indicating a general similarity to the thermal reaction.

3) The Effect of Excess Base Concentration on Tosylhydrazone Decompositions

The effect of an excess of strong base at low temperatures has recently been reported simultaneously by Shapiro and Heath[7] and by Friedman and coworkers[8]. The former prepared olefins in good yield from aliphatic toluene-p-sulphonylhydrazones containing α-hydrogen atoms, by using two or more equivalents of strong base at room temperature. For example, a quantitative yield of 2-bornene was obtained from camphor tosylhydrazone:



Scheme (3)



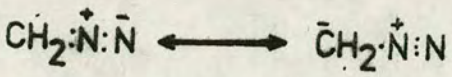
In contrast to the previous studies[2-5], these workers[7], proposed a third mechanism for the decomposition involving a carbanionic intermediate, which was supported by deuterium-labelling studies (scheme (3)). Friedman[8] reported similar results.

II DIAZOALKANES AND DIAZOALKENES[9]

Since diazoalkanes are the primary products in the decomposition of tosylhydrazone salts, it would be of value to consider now some of the properties of diazoalkanes and diazoalkenes. These compounds have been known for many years, and consequently many of their reactions have been fully investigated[10].

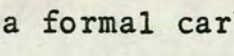
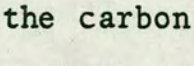
1) Stability and Structure

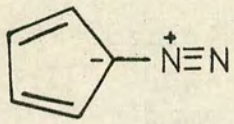
Diazomethane is the simplest diazoalkane and is best represented as a resonance hybrid, having contributions from linear structures with opposing dipoles:



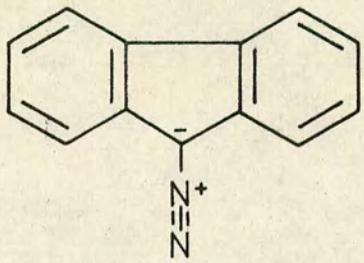
It is extremely unstable, highly toxic and therefore difficult to work with.

The stability of its analogues depends markedly on the nature of the substituents. Conjugating substituents, whether electron-releasing or electron-withdrawing increase the stability. Thus, diazoalkanes and diazoalkenes having carbonyl, aryl and nitrile, or other conjugating substituents are relatively more stable. Thus, diazocyclopentadiene and diazofluorene are both stable thermally. The latter, for example requires a temperature of 140° to induce rapid decomposition.

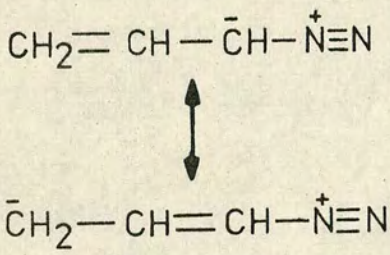
Electron-withdrawing substituents favour a resonance structure having a formal carbanion centre  whereas electron-releasing substituents favour a formal positive charge on the carbon atom  . Thus, diazocyclopentadiene, 9-diazofluorene, 3-diazopropene and α-diazocarbonyl compounds are in the former category whereas/...



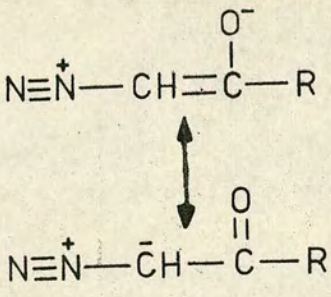
diazocyclopentadiene



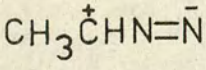
9-diazofluorene



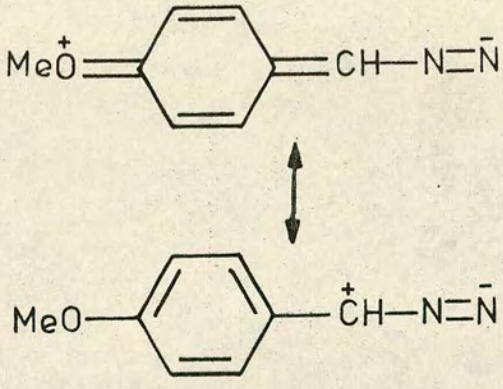
diazopropene



α-diazoketone



diazoethane



p-methoxyphenyldiazomethane

whereas diazoethane and p-methoxyphenyldiazomethane are examples of the latter.

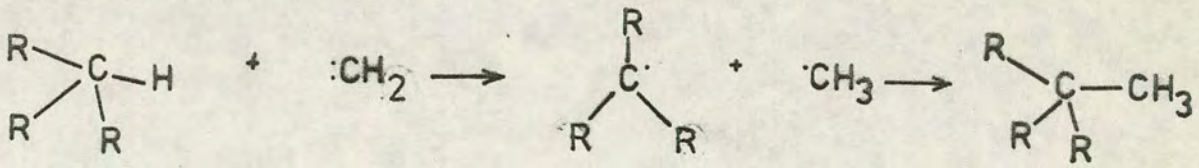
2) Carbene Formation[11,12]

The photolysis or thermolysis of diazoalkanes in aprotic solvents provide the most common general route to carbenes. Photochemically generated carbenes are highly energetic species and their reactions may be indiscriminate. For this reason, photolysis of diazocompounds is often not a good method for generating carbenes for synthetic purposes. Thermal decomposition may produce a less energetic carbene, but has the disadvantage that other modes of reaction of the diazocompound, not involving carbenes, become important (see section II.3 below). Also, some diazoalkanes are rather stable thermally and consequently reaction temperatures may be high: 9-diazofluorene and diazocyclopentadiene derivatives are in this category. However, in aprotic solvents, carbenes are generally produced. These can then undergo any or all of the following reactions: cycloaddition to double and triple bonds, insertion into carbon-hydrogen bonds, rearrangement, abstraction or reaction with diazoalkane precursor to form an azine. The types of reaction undergone by a specific carbene can be correlated with its electronic structure. This correlation viz that singlet carbenes generally undergo concerted reactions whereas triplet carbenes undergo stepwise/...

stepwise reactions has been well documented[11,12], and will not be fully discussed here. Skell[13], and later Woodward and Hoffmann[14] have made the most significant advances in the theoretical treatment and rationalisation of reactions in this field.

Insertion reactions of carbenes can be stereospecific or non-stereospecific corresponding to concerted[15] and non-concerted[16] mechanisms respectively. The concerted process involves a three-centre transition state:

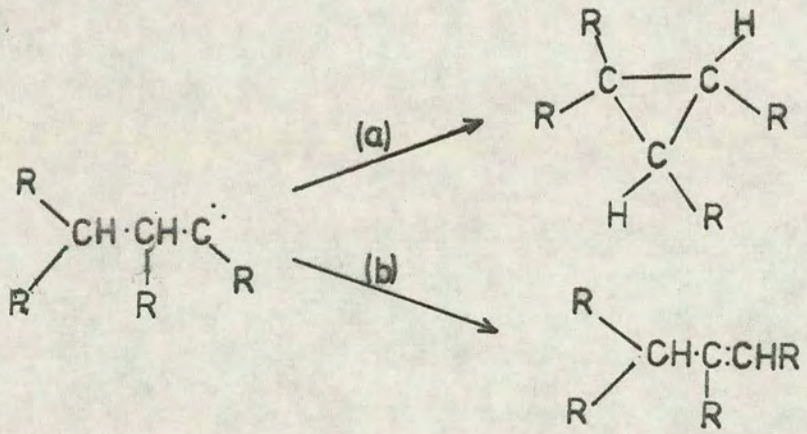
and the configuration of the substrate is retained. The non-concerted alternative is an abstraction-recombination process:



Since this mechanism involves radical intermediates, the configuration of the substrate will be lost, and other products might well be expected. However, the re-

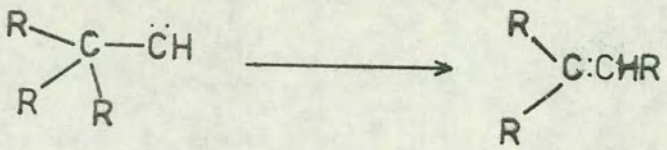
combination/...

recombination could still be very efficient, if the radicals were held together in a solvent cage, for example. In this case, the configuration of the substrate may not be completely lost. There is experimental support for both mechanisms, but in the main, this is inconclusive. Two important types of carbene insertion reaction are: (a) insertion into a β-carbon-hydrogen bond to form a cyclopropane, and (b) insertion into an α-carbon-hydrogen bond to form an olefin:

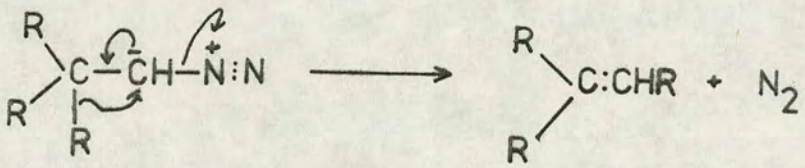


These reactions often occur in competition with one another.

1,2-Shifts of alkyl groups are also quite common:

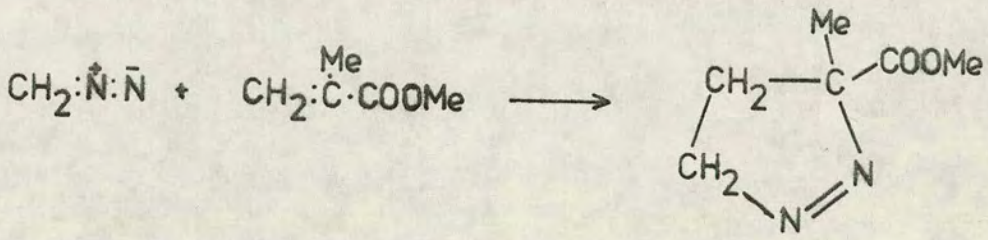


However, it is often difficult to distinguish between this mechanism and one involving concerted migration of the group R and expulsion of the leaving group:



3) Cycloaddition and Electrocyclic Reactions of Diazocompounds

Diazocompounds have been known for many years to react with alkenes and alkynes to form five-membered heterocyclic compounds:



However, it was not until the early 1960's that the classification of 1,3-dipolar cycloaddition became accepted[17]. This followed a series of outstanding studies by Huisgen[18-20] and his collaborators, in which diazoalkanes were shown to represent just one example of a wider/...

wider class of 1,3-dipolar molecules, (a-b-c), which undergo 1,3-cycloadditions and are described by Zwitterionic octet structures:

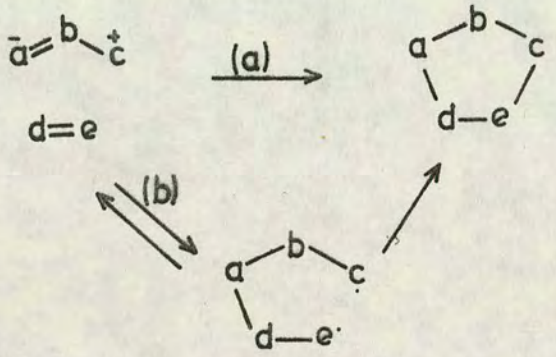
$$a{:}\overset{+}{b}{\cdot}\overset{-}{c} \longleftrightarrow \overset{-}{a}{:}\overset{+}{b}{:}c \qquad (b=N)$$

$$a{:}\overset{+}{b}{\cdot}\overset{-}{c} \longrightarrow \overset{-}{a}{:}\overset{+}{b}{:}c \qquad (b=NR, O)$$

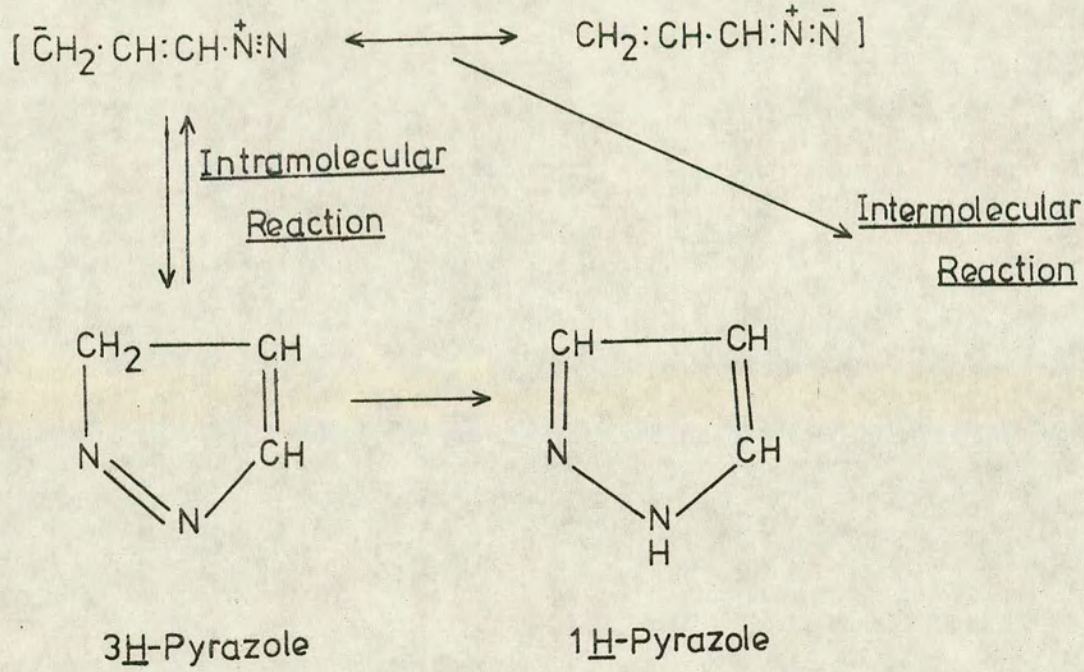
Specific classes of molecular 1,3-dipoles include diazoalkanes ($R_2C{=}\overset{+}{N}{=}\bar{N}$), nitrile oxides ($ArC{\equiv}\overset{+}{N}{-}\bar{O}$), azides ($ArN{=}\overset{+}{N}{=}\bar{N}$), nitrones ($ArCH{=}\overset{+}{N}(Me){-}\bar{O}$) and nitrile amines ($ArC{\equiv}\overset{+}{N}{-}\bar{N}{-}Ar$). The importance of these 1,3-dipoles lies in their usefulness in heterocyclic synthesis. 1,3-Dipolar cycloadditions exhibit common mechanistic features[18]: they are not markedly influenced as to rate or stereochemistry by solvent polarity and they show low enthalpies of activation and large negative entropies of activation. Five-membered heterocycles, in which the stereochemistry of the reacting olefin (dipolarophile) is retained, are formed. Finally, reaction rates are markedly increased by conjugation of the reacting site in the dipolarophile, but reduced by the steric effects of all types of substituent. Reactivity of diazoalkanes, is, on the other hand, reduced by conjugating substituents but increased by substitution of alkyl groups.

Apart from the obvious synthetic value of these cycloadditions, there has been considerable interest in the reaction/...

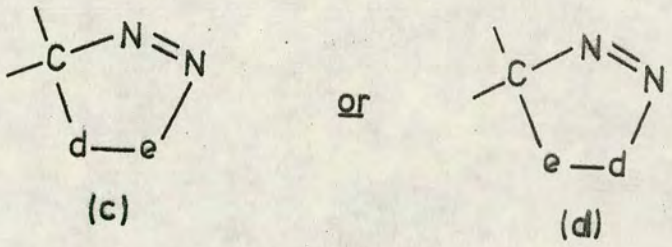
reaction mechanism. Basically, the problem is to decide between a concerted or two-step mechanism:



A two-step mechanism involving polar intermediates had seemed unlikely because of the lack of any clearly-defined dependence of reaction rate on solvent polarity. However, Firestone[21] has recently argued cogently in favour of a two-step mechanism involving diradical intermediates (route (b)). Huisgen[18] on the other hand proposed that 3+2 cycloadditions of diazoalkanes occurred via concerted processes involving cyclic transition states. Woodward and Hoffmann's work[14] on the conservation of orbital symmetry has supplied a theoretical basis, and, taken with most of the experimental data provides overwhelming support for Huisgen's earlier predictions. It must be noted however, that the relative orientation (whether (c) or (d)) is not adequately predicted by either mechanism;


[$\bar{C}H_2 \cdot CH:CH\cdot\overset{+}{N}:N$
$CH_2:CH\cdot CH:\overset{+}{N}:\bar{N}$]
Intramolecular Reaction
Intermolecular Reaction
CH_2
CH
N
CH
N
CH
CH
N
CH
N
H
3H-Pyrazole
1H-Pyrazole

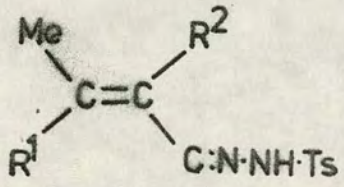
Scheme (4)



(c) (d)

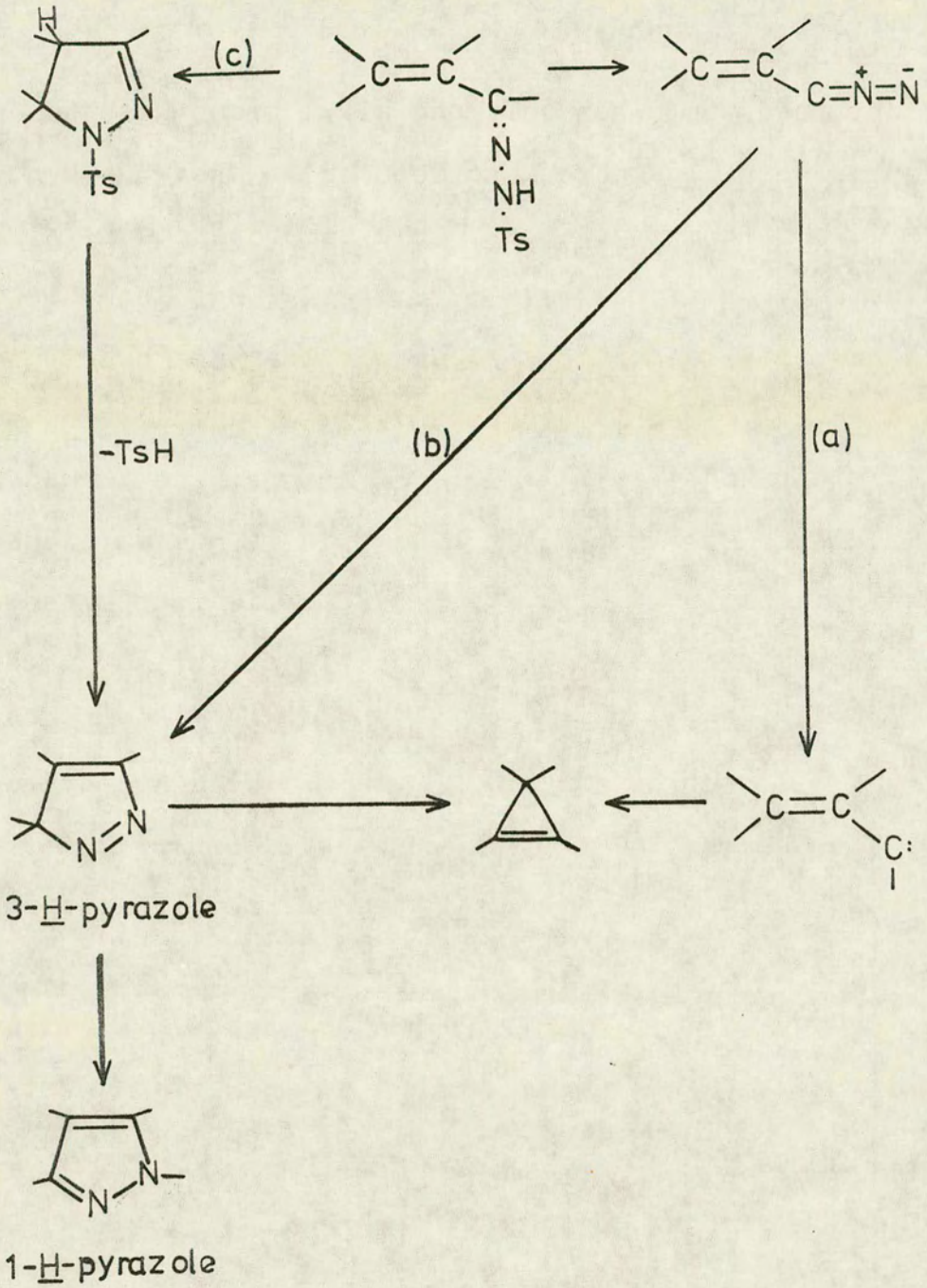
and generally, a mixture results.

Of more relevance to this work is the case where both olefin and diazo groupings are present in the same molecule. Here, an intramolecular cycloaddition, a so-called electrocyclic ring-closure, occurs to form, for example a pyrazole (scheme (4)). The first reports of this type of reaction were those of Closs, Closs and Böll[22] who studied the base-induced decompositions of toluene-p-sulphonylhydrazones of general type V:



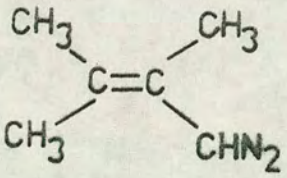
(V)

They found that these decompositions gave mainly cyclopropenes when the β-carbon atom was substituted by two alkyl groups, but also that pyrazoles could be obtained by varying the substituents at that carbon atom. Thus, when the β-carbon atom was substituted with two alkyl groups, yields of cyclopropenes upwards of 50% were/...

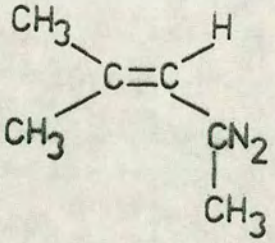


Scheme (5)

were obtained, but when only one alkyl group was present, cyclopropene yields were much reduced. When two hydrogen atoms were in the β-position, no cyclopropene was formed, but instead, an aromatic 1H-pyrazole. This lead Closs, Closs and Böll to consider three working hypotheses as to the actual mechanism (scheme (5)). By following route (a), cyclopropene formation is *via* the carbene formed in turn from the intermediate diazoalkene. However, the diazoalkene could undergo an electrocyclic ring closure to the 3H-pyrazole which could then react further under the reaction conditions to form the cyclopropene by nitrogen elimination or the 1H-pyrazole by a 1,5-hydrogen shift when there is a hydrogen atom attached to the β-carbon (route (b)). Route (c) forms a third possibility, leading ultimately to a stable pyrazole when a β-hydrogen atom is present. By lowering the reaction temperature to 70-90° from *ca* 160° these workers went on to isolate the diazoalkenes VI and VII:

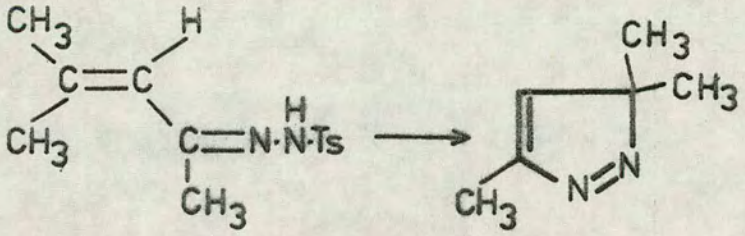


(VI)

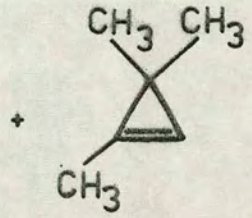


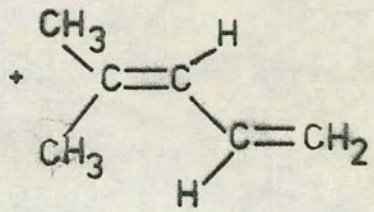
(VII)

These both yielded 1,3,3-trimethylcyclopropene on pyrolysis. However, by careful variation of the reaction conditions, Closs, Closs and Boll[11] managed to obtain 3,3,5-trimethyl-pyrazolenine (IX) from the sodium salt of VIII.



(VIII) (IX)





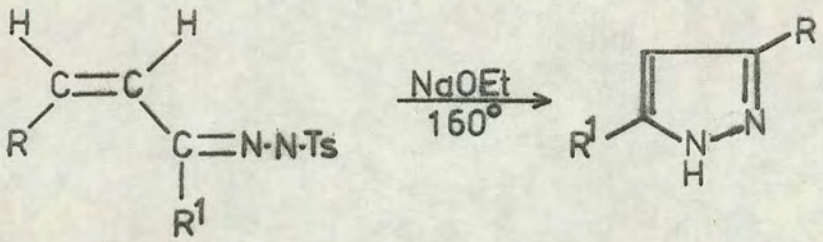
(X)

Compound (IX) was resistant to pyrolytic cleavage at temperatures at which cyclopropene-formation from the sodium salt proceeded smoothly, a result which eliminated the possibility of 3H-pyrazoles being intermediates in cyclopropene-formation/...

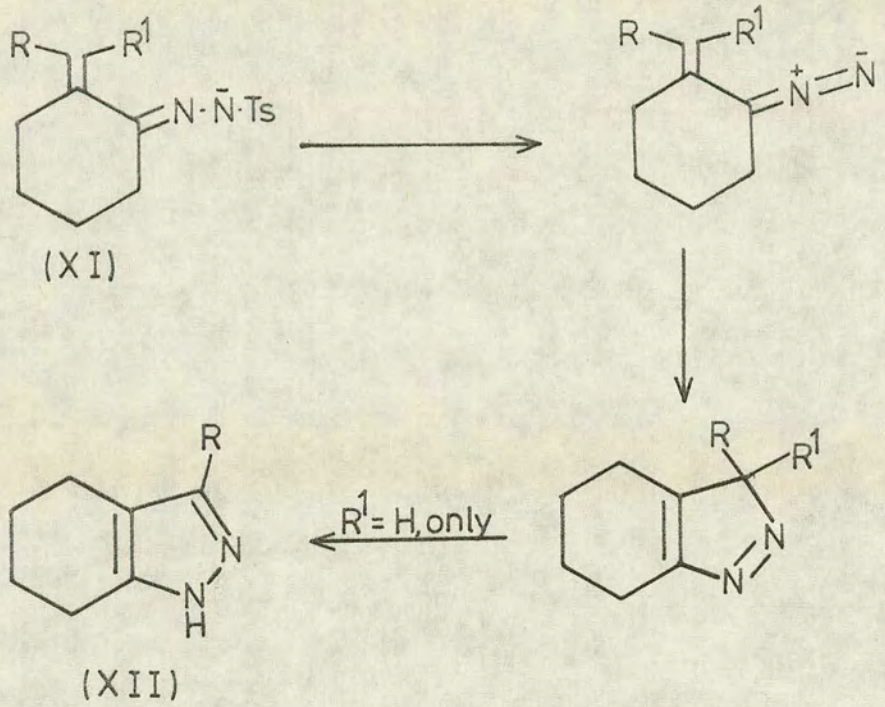
cyclopropene-formation, and simultaneously constituted strong evidence for the carbenic route. Formation of some diene (X) in the decomposition of the sodium salt (VIII) backed up the carbene hypothesis. These workers preferred route (c) as the cyclisation pathway since in one case, the diazoalkene was formed simultaneously with the 3H-pyrazole under conditions where both diazocompound and pyrazole are stable. To account for the large variation the the yields of cyclopropenes, Closs suggested that the relative rates of the various steps in the reaction scheme were strongly dependent on the degree of substitution at the β-carbon atom. Both steric and electronic effects resulting from increasing methyl substitution should retard the rates of the cyclisation steps whereas the elimination steps (resulting in diazoalkene and carbene formation) should be accelerated by the electron-releasing power of the alkyl groups. The resulting shift of the product balance in favour of heterocyclic compounds with decreasing methyl substitution then corresponds to the experimental observation.

Bartlett and Stevens[23] studied the base-induced decomposition of the toluene-p-sulphonylhydrazones of α,β-unsaturated ketones containing a hydrogen atom and/or phenyl group at the β-carbon atom, and found that the tosylhydrazones of crotonaldehyde cinnemaldehyde and methylstyrylketone/...

methylstyrylketone all gave the corresponding pyrazole in good yield:



Closs and coworkers[22] also reported that the decomposition of crotonaldehyde tosylhydrazone in diglyme gave only 3% of 3-methylcyclopropene, the major product being the pyrazole (yield not quoted). The work of Bartlett and Stevens therefore tends to support Closs's suggestion that increasing substitution of the β-carbon atom decreases the yield of cyclopropene while increasing the yield of heterocyclic. Brewbaker and Hart[24] have examined the mechanism of pyrazole formation and concluded that ring-closure occurs via an intramolecular 1,3-dipolar cycloaddition of the diazoalkene, and that the observed products, the more stable aromatic 1H-pyrazoles were subsequently formed by a hydrogen-migration. Phenyl, and very occasionally methyl-migrations have been observed[25] in such an aromatisation step. These migrations can be thermally induced[26] or acid-catalysed[27].

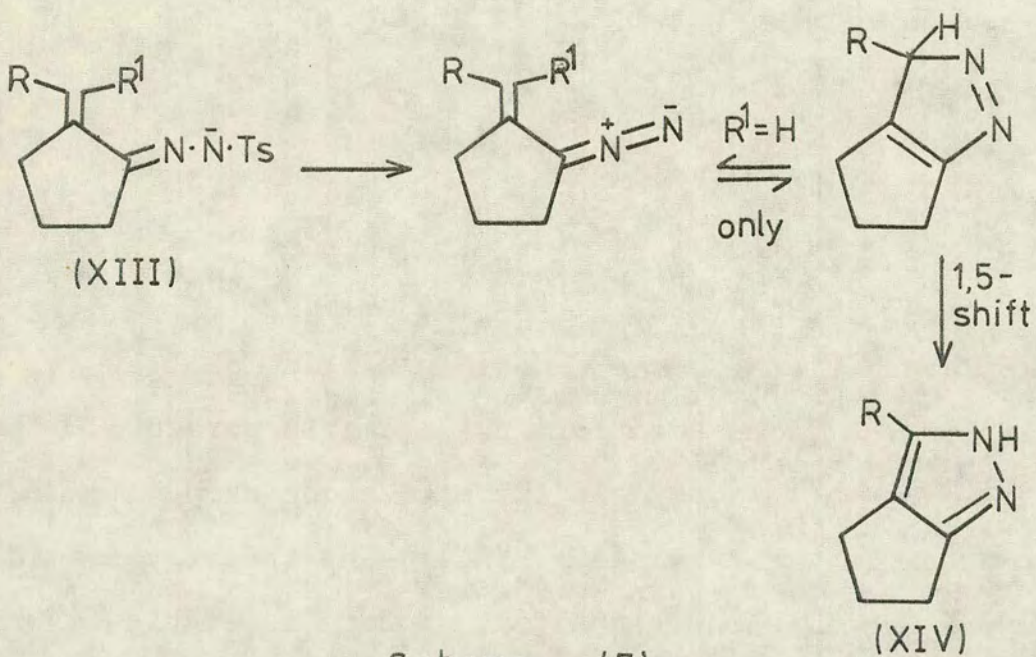


a) R, R^1 = $-(CH_2)_5-$ 87%

b) R, R^1 = Ph 73%

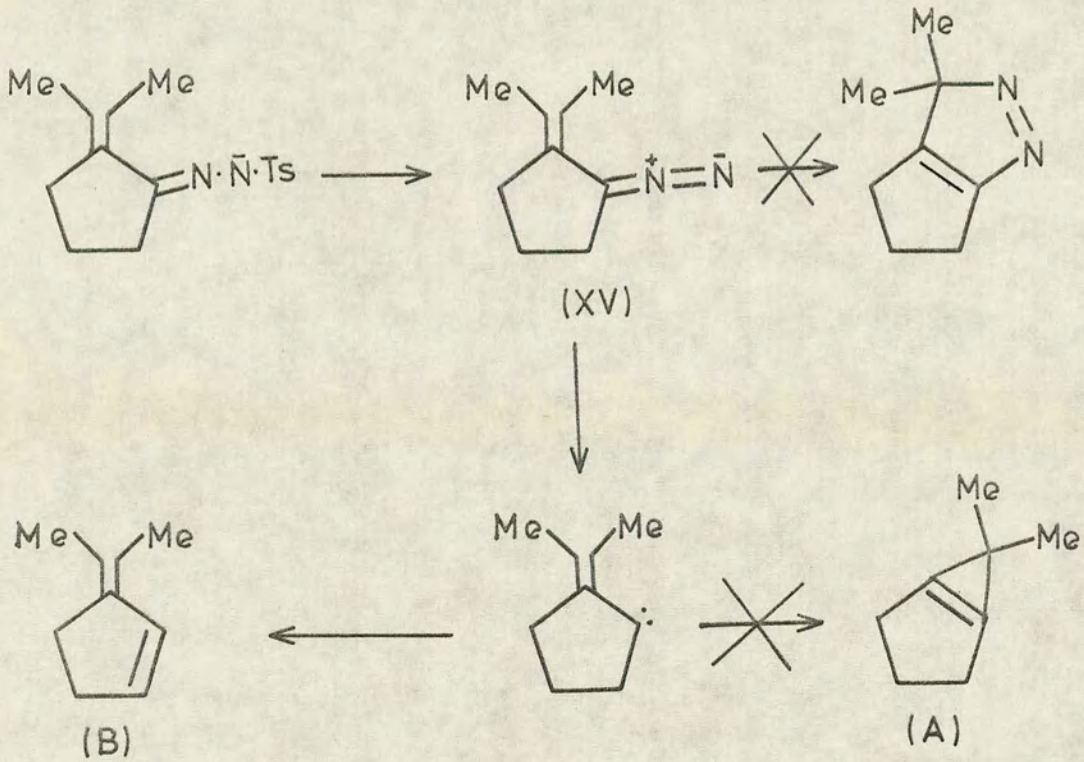
c) R = Ph, R^1 = H 77%

Scheme (6)

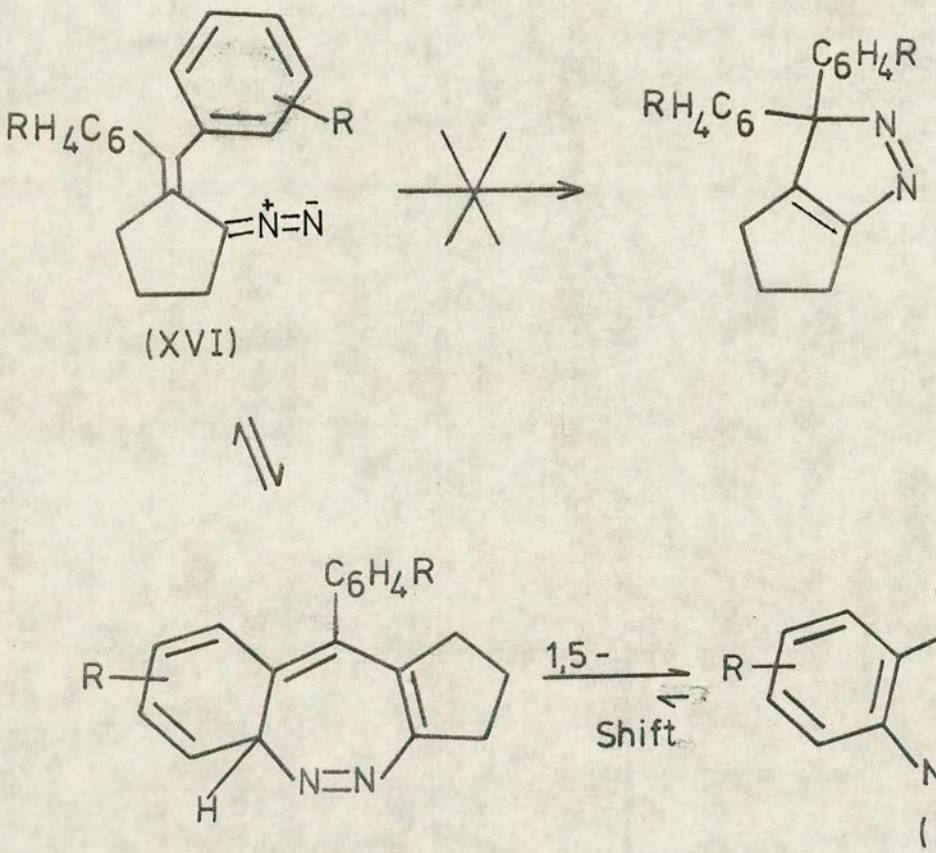


Scheme (7)

In 1970, Sharp and coworkers[28] reported the base-induced decomposition of the tosylhydrazones of some 2-methylene-cyclohexanones (XI) and 2-methylenecyclopentanones (XIII). The former derivatives were found to cyclise in an analogous manner to that described above and pyrazoles (XII) were the observed products (scheme (6)) but the cyclopentanone analogues cyclised to pyrazoles only when R'=H to give the aromatic 1H-pyrazoles (XIV) (scheme (7)). When R,R' were both methyl groups, the diazoalkene intermediate in the cyclopentanone series reacted only *via* loss of nitrogen to afford carbene-derived products (scheme (8)) whereas in the cyclohexanone series pyrazoles were still formed. This suggested that the absence of cyclisation in the cyclopentanone derivatives was a steric and not a substituent effect and was presumably due to the greater distance between the ends of the π-system and to the greater blocking effect of the alkyl group in the more rigid methylenecyclopentane system. These two effects then combined to prevent (XV) attaining the transition state required for cyclisation. Furthermore, Sharp and Thorogood[25] suggested that the cyclisation step was reversible, and that this was followed by a 1,5-shift of the group R to form the aromatic pyrazole. When R or R'=H, this is a facile aromatisation step which is not possible when R=R'=Me. This means that cyclisation can only occur when the initial product is stable or when it/...



Scheme (8)



a) R = H, 80% ; b) R = p-CH_3, 68% ; c) R = p-F, 44%.

Scheme (9)

it can undergo a rapid 1,5-hydrogen shift to a stable product. Cyclopropenes of type (A) (scheme (8)) are not formed due to their inherent instability, but instead, the carbene intermediate undergoes a 1,2-hydride shift to the diene (B).

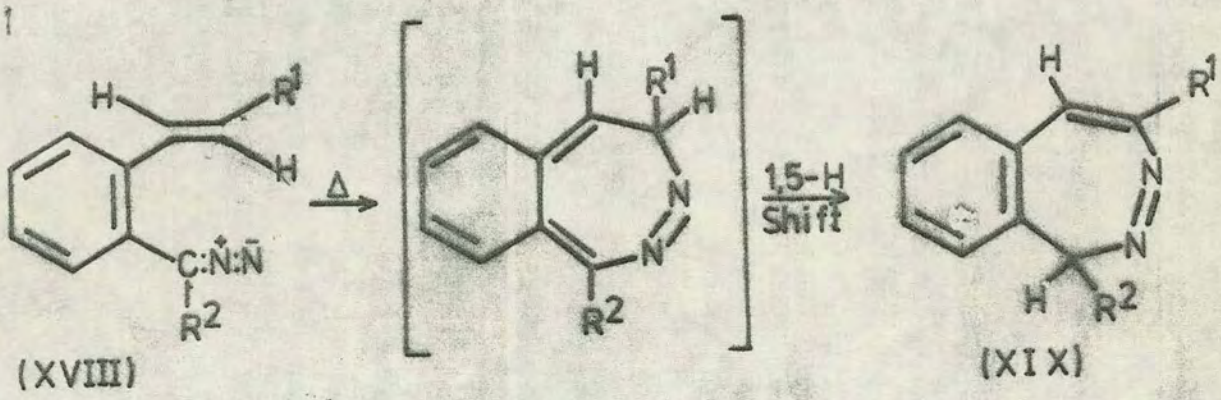
When R and R' are both aryl groups, the decomposition takes yet a third pathway viz cyclisation of the diazo-compound (XVI) onto the o-position of the cis-aromatic ring, thus providing a route[28] to the otherwise inaccessible[29] 1,2-benzodiazepines (XVII), (scheme (9)). Here again, it was postulated that the diazoalkene was unable to cyclise to the pyrazole for steric reasons. Sharp and coworkers[28] dismissed the possibility of intramolecular nucleophilic attack on the benzene ring by the tosylhydrazone anion for two reasons:

i) the diazoalkene (prepared from the photolysis of the sodium salt) cyclised to the benzodiazepine in the absence of base suggesting that the reaction involved a thermal cyclisation of the diazoalkene;

ii) when the decomposition was carried out in the presence of tributylphosphine, the characteristic red colouration of the diazoalkene was not observed, and no diazepine was obtained. Instead the diazoalkene was intercepted by a fast reaction with the phosphine to give/...

give a phosphazine which hydrolysed during work-up to give 2-diphenylmethylenecyclopentanone hydrazone (85%). These results indicated that diazepine-formation involved cyclisation of the diazoalkene intermediate and not direct cyclisation of its tosylhydrazone salt precursor.

Sharp and Thorogood[26] then investigated the decomposition of some α-(o-alkenylaryl)diazoalkenes (XVIII) which were obtained from the toluene-p-sulphonylhydrazones of some 2-acylstyrenes and 2-acylstilbenes. Here, the diazoalkene underwent an electrocyclic ring closure onto the styrene/stilbene double bond, and this was followed by a rapid 1,5-sigmatropic hydrogen migration to give a 1H-2,3-benzodiazepine (XIX).



(XVIII) (XIX)

Development of this work lead to a convenient synthesis of the previously unknown 1H-2,3-benzodiazepines and their 5H-isomers[30].

B) THERMAL AND PHOTOCHEMICAL DECOMPOSITIONS OF AZOCOMPOUNDS

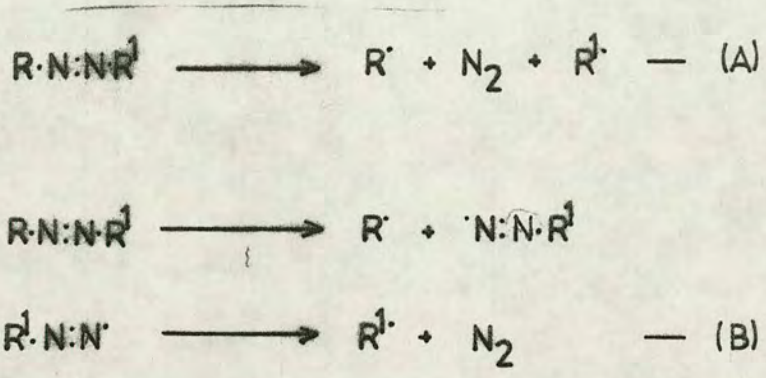
Azocompounds have been known for many years, and their importance has stemmed from the fact that many aromatic azocompounds which can readily be prepared by the diazo-coupling method[31], are highly coloured and suitable for use as dyestuffs. Their importance in organic chemistry arises from the fact that the azoalkanes act as a convenient source of alkyl radicals which are formed both on thermolysis and photolysis[32].

Azocompounds can exist in cis- and trans-forms, the trans-isomers being the more stable thermodynamically. However, trans/cis-isomerisation can be induced by photolysis of the trans-isomers: trans-azobenzene, for example, produces an equilibrium mixture of the cis- and trans-isomers. The cis-forms readily thermally isomerise back to the more stable trans-isomers by a non-radical route[33,34].

Cyclic azocompounds on the other hand usually exist in the cis-form, although Overberger[35] has recently prepared eight, nine and ten-membered trans-cyclic azocompounds by photolysis of the normal cis-isomers. The reason that cyclic compounds exist as cis-forms is the greater ring strain which would exist as a consequence of the trans-azo linkage contained in a ring.

I. DECOMPOSITION OF ACYCLIC AZOCOMPOUNDS

Over the years, two reaction schemes have dominated the literature for the decomposition of azocompounds into two free radicals and nitrogen:



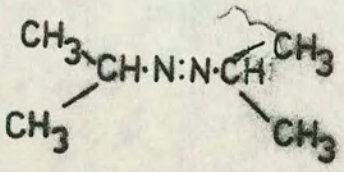
$$R{\cdot}N{:}N{\cdot}R^1 \longrightarrow R^{\cdot} + N_2 + R^{1\cdot} \quad \text{— (A)}$$

$$R{\cdot}N{:}N{\cdot}R^1 \longrightarrow R^{\cdot} + {\cdot}N{:}N{\cdot}R^1$$

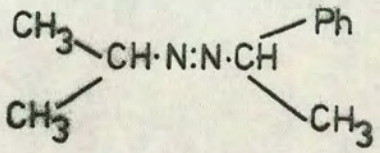
$$R^1{\cdot}N{:}N^{\cdot} \longrightarrow R^{1\cdot} + N_2 \quad \text{— (B)}$$

Scheme (A) implies simultaneous scission of both carbon-nitrogen bonds with formation of three fragments in the rate-determining step, whereas scheme (B) implies breakage of only one of the C-N bonds in the rate-determining step. The direction of bond-cleavage in the second case depends very much on the relative strengths of the two C-N bonds and also on the relative stabilities of the free radicals formed. A choice has generally been made between these mechanisms rather than application of a rigorous proof. Usually, scheme (A) has been applied to symmetric azocompounds and scheme (B) to unsymmetric compounds. For example, Cohen and Wang[36] and Overberger and DiGuilio[37] have advanced detailed discussion on the question/...

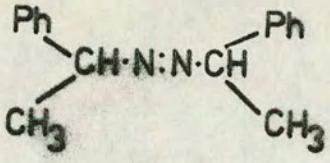
question of whether carbon-nitrogen bond cleavage is simultaneous or stepwise. Comparisons of activation energies and reaction rates were made for the decomposition of compounds (XX) - (XXII).



(XX)



(XXI)

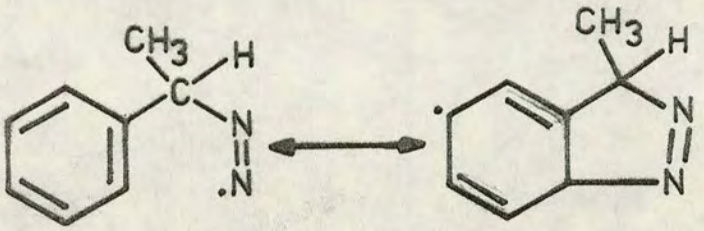


(XXII)

Because the activation energy decreased by about 4 k. cal. $mole^{-1}$ each time a phenyl group replaced a methyl group in the series and because the ratio of the rates for (XXII) and (XXI) was greater than a statistical factor of two, these authors[36, 37] concluded that both carbon-nitrogen bonds were breaking simultaneously. The increase in rate and decrease in activation energy is due to the phenyl group aiding in the delocalisation of a lone electron in the transition state. This argument holds only if it can be shown that the presence of an

α-phenyl/...

α-phenyl group cannot also stabilise the formation of the nitrogen-containing intermediate (XXIII) which could possibly be stabilised by delocalisation of the free electron as follows:

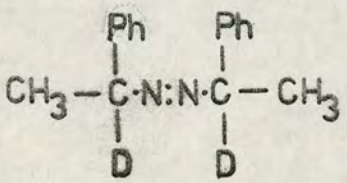


(XXIII)

However, in order that the phenyl group participate in this manner, it is necessary that the ortho-hydrogen be displaced somewhat out of the plane of the benzene ring leading to loss of aromaticity as the reactant molecule moves along its path to the transition state. This suggests that (XXIII) will be destabilised by such an interaction.

Seltzer[38] approached the problem in a different way which was to measure the secondary α-deuterium isotope effect in the decomposition of azo-bis-(α-phenyl)ethane-α,α'-d_2. It is known[39] that the rate of S_N1 solvolysis for compounds having α-deuterium atoms at the site of substitution is slower by about 15% at room temperature. Conversely, reactions which involve addition of a fragment to a trigonal reaction site bearing α-deuterium atoms/...

atoms proceed at a faster rate than their protium analogues.[40] Furthermore, there have been indications[41, 42] that the isotope effect for two deuterium atoms at a reaction site is twice that for one deuterium atom. Seltzer[38] argued therefore that it seemed reasonable that two α-deuterium atoms at separate sites would produce an isotope effect similar to that observed for two atoms of deuterium at one reaction site if both centres of reaction were undergoing change simultaneously in the rate-controlling step. To verify this, he therefore synthesised azo-bis(α-phenyl)ethane-α,α'-d_2 (XXIV) and measured its rate of decomposition in ethylbenzene, and compared this with the natural compound under identical conditions.



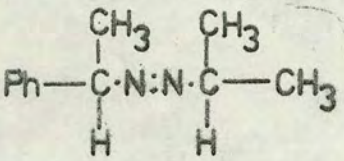
(XXIV)

The observed isotope effect was $k_H/k_D = 1.18 \pm 0.02$ when only 72% of the atoms in each α-position were deuterium. The expected[43] effect for two fully deuterated α-positions is 1.27 ± 0.03 while that for only one deuterium is 1.12. Thus, if stepwise path is

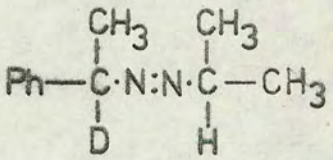
followed/...

followed, an isotope effect of 1.12 would be expected whereas simultaneous C-N bond scission would result in an isotope effect of 1.27. The observed isotope effect (after normalisation for two α-deuterium atoms) corresponds to a transition state in which both carbon-nitrogen bonds are undergoing simultaneous cleavage i.e. scheme (A) holds in this case.

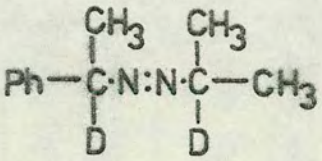
Seltzer[44] then went on to investigate the secondary kinetic isotope effect in the series of unsymmetric compounds (XXV), (XXVI) and (XXVII).



(XXV)



(XXVI)

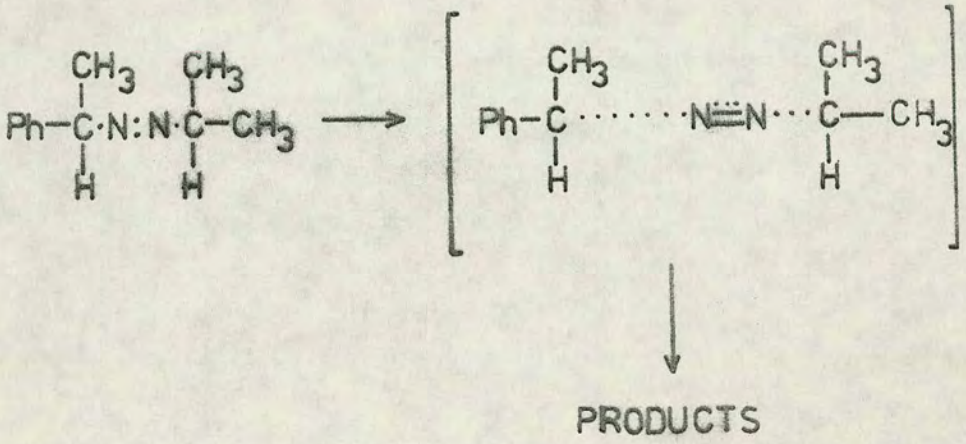


(XXVII)

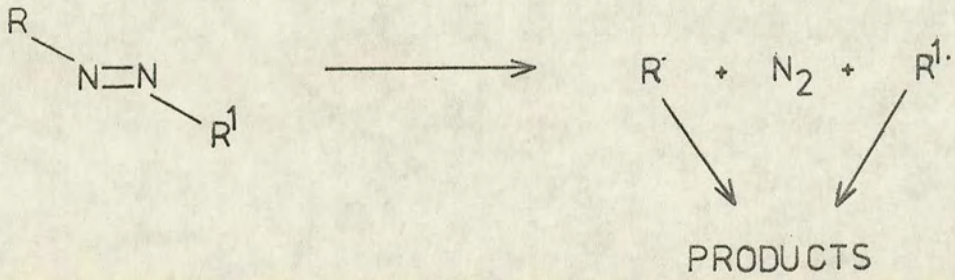
The values he obtained were $k_{XXV}/k_{XXVI} = 1.16$ and $k_{XXV}/k_{XXVII} = 1.04$.

If the decomposition proceeds <u>via</u> simultaneous scission (scheme A), then both these rate constant ratios would be/...

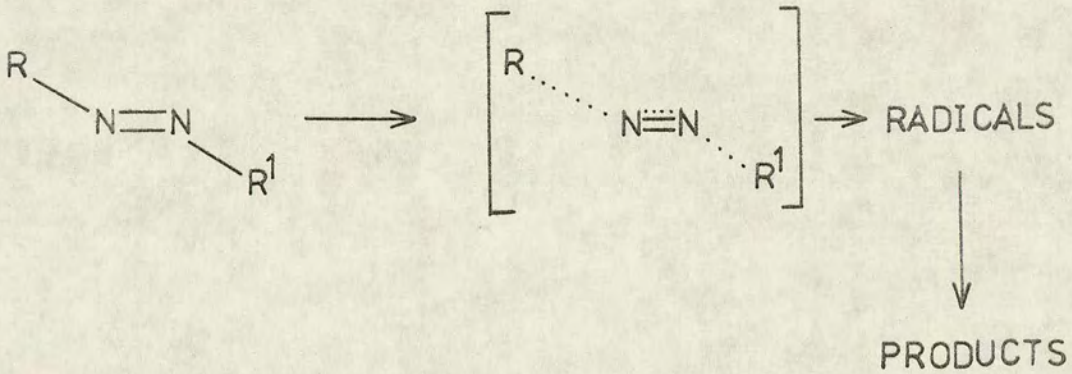
be expected to be equal to the theoretical value of 1.15, whereas the stepwise mechanism, (scheme B), would require one of these ratios to be 1.15 and the other to be unity, depending on which bond is breaking first. The observed values are such that the reaction scheme must be considered as being intermediate between (A) and (B) i.e. simultaneous rupture of both C-N bonds, but such that the azo-propane bond rupture is not as advanced as that of the azo-(α-phenyl)ethyl bond. This means that the reaction proceeds through a transition state as follows:



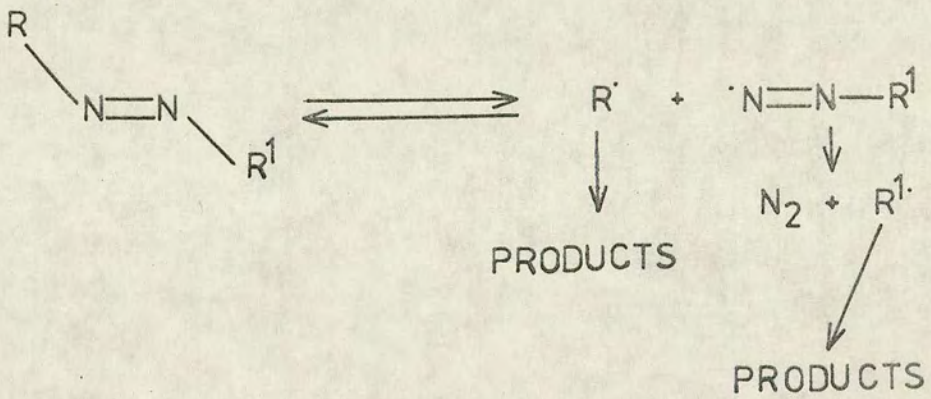
In a third similar study, Seltzer and Dunne[45] studied the decomposition of the more unsymmetrical compounds (XXVIII), (XXIX) and (XXX):



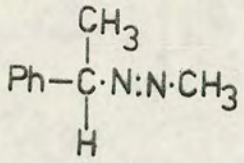
Scheme A_1



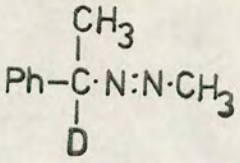
Scheme A_2



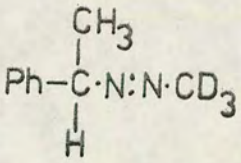
Scheme B



(XXVIII)



(XXIX)



(XXX)

and here, their kinetic isotope measurements supported a two-step mechanism in which the rate controlling step was the separation of α-phenylethyl and azomethyl radicals.

Thus, for the thermolysis of acyclic azocompounds in solution, there appear to be three possible mechanisms:

A_1 - simultaneous scission of both C-N bonds in symmetric azocompounds;

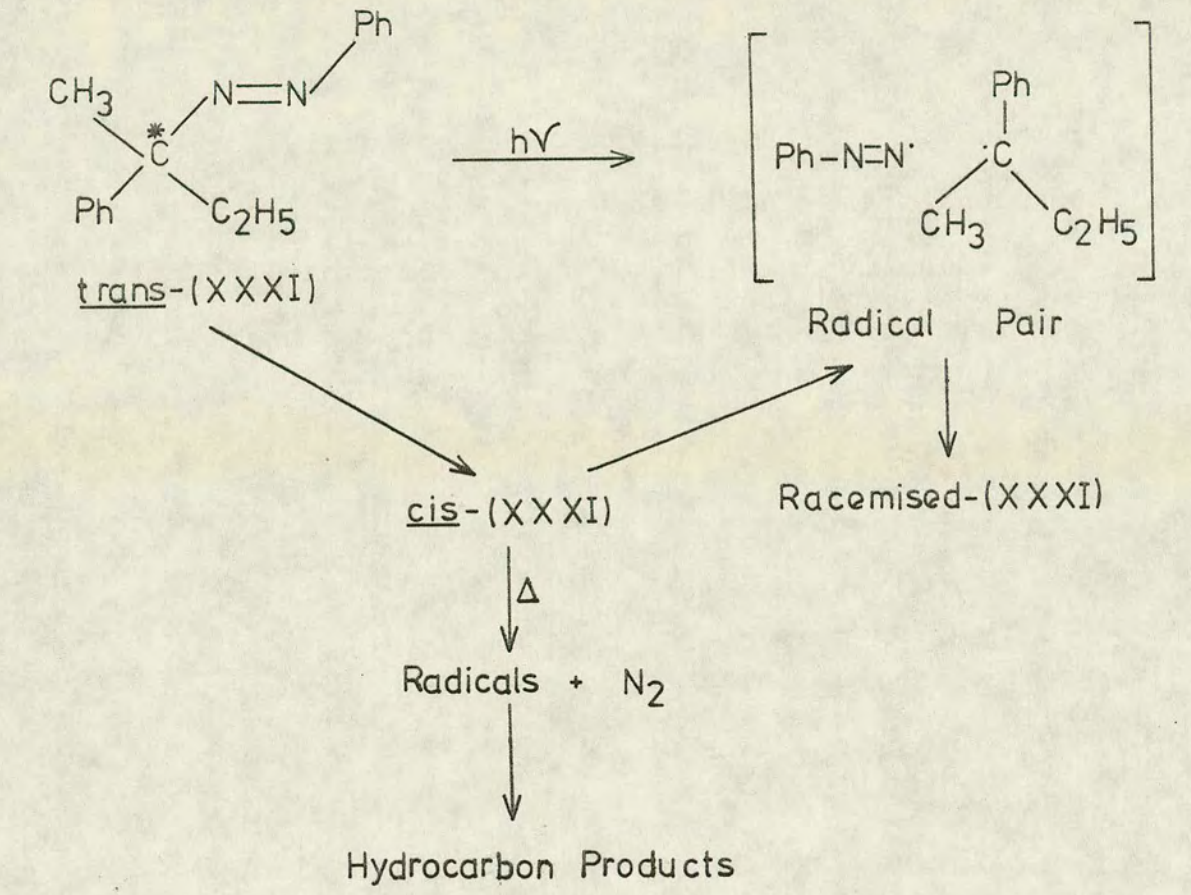
A_2 - simultaneous scission of both C-N bonds, but with one bond-rupture distinctly more advanced than the other in slightly unsymmetrical azocompounds;

B - stepwise decomposition by scission of only one C-N bond in very unsymmetrical azocompounds.

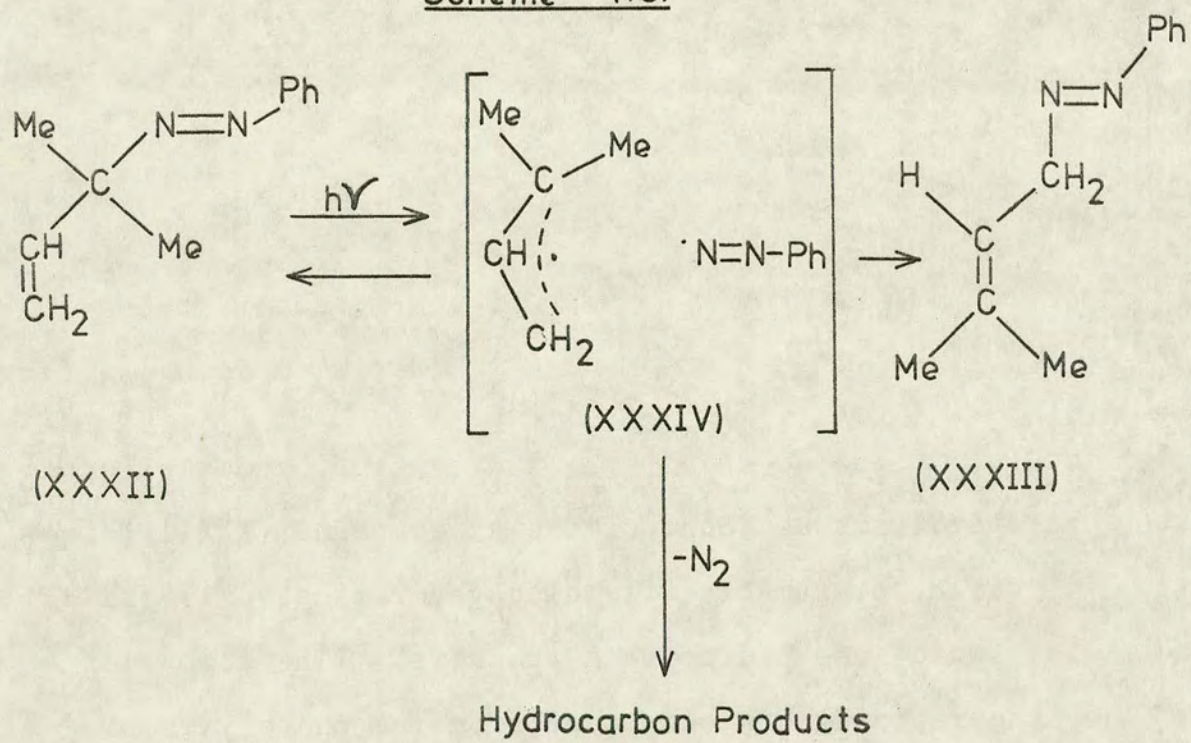
These mechanisms also apply to the photolysis of this type of compound.

Recently, Porter and coworkers[46] have accumulated some evidence for the intermediacy of the nitrogen-containing radical, R-N=N$^{\cdot}$, in the photolysis of an unsymmetric azo-

compound/...

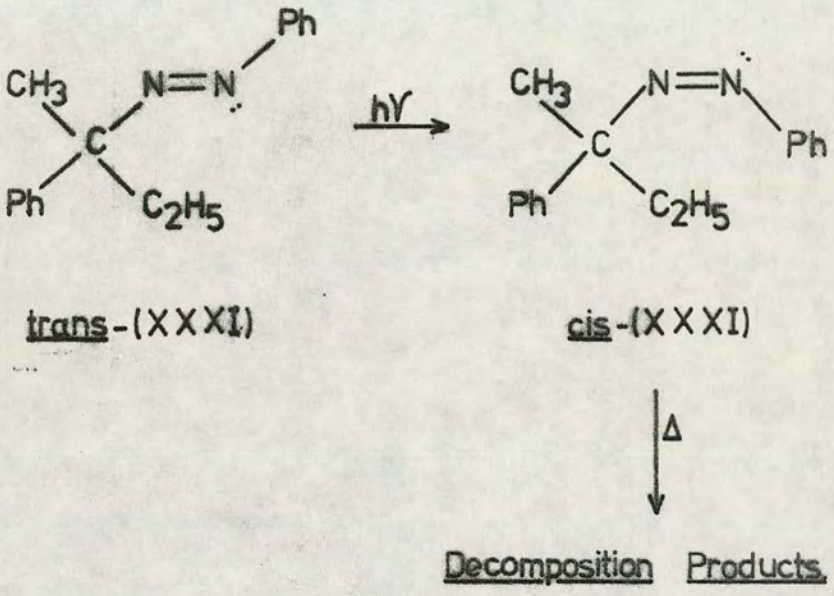


Scheme (10)



Scheme (11)

compound. They synthesised the optically active compound trans-(XXXI) and photolysed it at 0°, in pentane, with 436nm light. This led to formation of the thermally unstable cis-isomer which underwent some thermal decomposition:



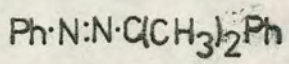
trans-(XXXI) cis-(XXXI)

At 40% completion, trans-(XXXI) was found to have been greatly racemised. This may be explained by scheme (10), since a bond to the assymmetric carbon atom is broken.

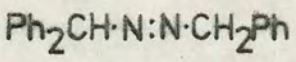
Porter and Iloff[47] have also synthesised, and studied the photolysis at 436nm of the azocompound (XXXII) in 20% yield, presumably via the caged radical-pair (XXXIV), along with some hydrocarbon products. The formation of the rearranged azocompound from the photolysis of (XXXII)/...

(XXXII) contrasts strongly with the photochemical behaviour of the symmetric azoanalogues. Thus, azobenzenes undergo only trans-cis photoisomerisation[48] whereas the symmetric dimethylallylazoanalogue of (XXXII) is reported[49] to photodecompose to give only free-radical coupling products, no rearranged azocompound being found.

Since the advent of the CIDNP effect in nmr spectroscopy, this phenomenon has been put to good use as regards the question of mechanism in the decomposition of unsymmetric azocompounds. For example, results obtained[50] for the decomposition of (XXXV) support the one-bond scission mechanism leading to a diazenyl radical intermediate, whereas results for (XXXVI) indicate either a concerted mechanism or a very short lifetime for the diazenyl radical:



(XXXV)



(XXXVI)

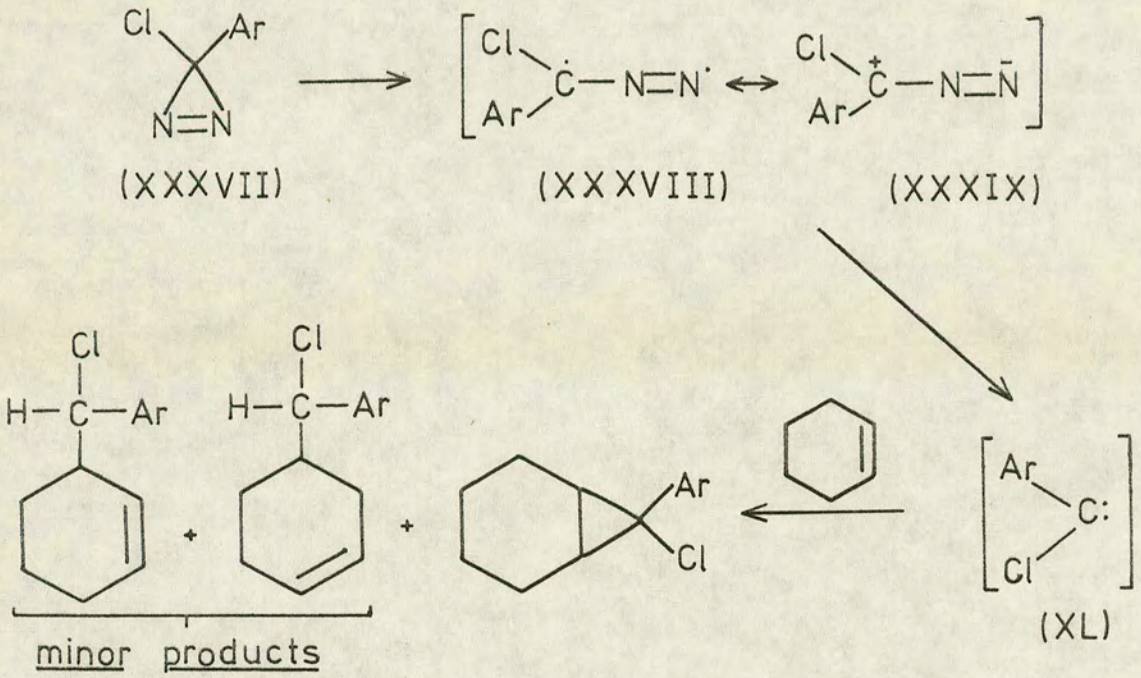
Crawford and coworkers[51-53] studied the gas phase decomposition of a series of eight acyclic azocompounds and from kinetic, product and kinetic isotope data, together with nitric oxide inhibited thermolysis, concluded that "... few, if any, of the azoalkanes undergo a concerted thermolysis to produce three fragments".

II DECOMPOSITION OF CYCLIC AZOCOMPOUNDS

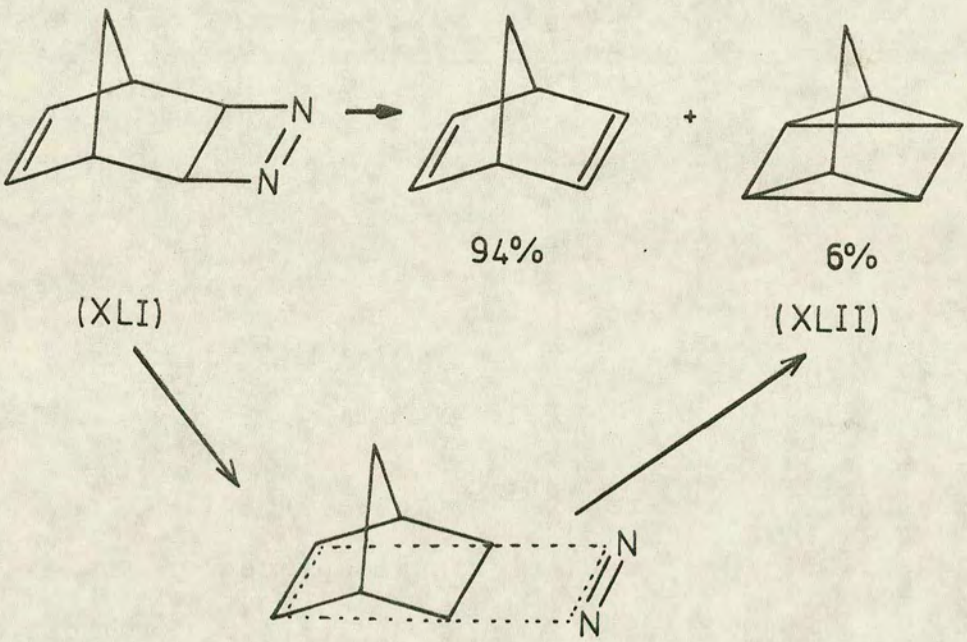
Cyclic azocompounds of many ring sizes have been prepared and decomposed either thermally or photochemically. The smallest possible ring system, the diazirine ring, has been prepared[54] and decomposed[55] while at the other extreme, Overberger and Lapkin[56] have prepared and studied the thermal decomposition of large cyclic bis-azocompounds of ring size 24 and 28 members. Between these extremes, 5-, 6- and, more recently, 7-membered compounds appear to have been most studied. Again, we have the controversy as to one-bond scission and two-bond scission mechanisms. In the former case, this can lead to either a nitrogen-containing diradical or a diazo-compound, depending on whether reaction is homolytic or heterolytic, and in the latter, a nitrogen-free diradical.

Liu and Toriyama[55] studied the thermal decomposition of a series of 3-chloro-3-aryldiazirines (XXXVII) in cyclohexene (non-polar), dimethylsulphoxide (polar aprotic) and di-ethyleneglycol monoethyl ether (polar protic) solvents. From their kinetic data, and lack of solvent effects for the series, they concluded that the mechanism involved the breaking of <u>one</u> of the diazirine C-N bonds. This leads to a diradical/dipolar intermediate (XXXVIII)/(XXXIX) in which the contribution of (XXXIX) is thought to be small, due to the lack of solvent effects on the de-

composition/...



Scheme (12)



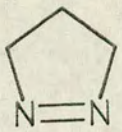
Scheme (13)

composition rate. The intermediate then expels nitrogen to form the carbene (XL) which goes on to react in the normal way (scheme (12)).

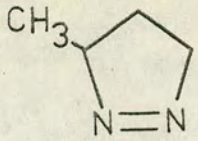
There appears to be only one example of decomposition of a four-membered cyclic azocompound in the current literature[57]. This involves the thermal decomposition of the tricyclic compound (XLI) which gives a 94% yield of norbornadiene, which is symmetry-forbidden, and only 6% of the thermally allowed product, (XLII) (scheme (13)). Presumably the ring strain associated with the transition state for formation of (XLII) is so high that reaction takes place preferentially by the lower energy process giving the symmetry-forbidden product.

The decomposition of pyrazolines and condensed pyrazoline ring systems have been studied greatly, notably by Crawford[58-62], Overberger[63-67] and Bergman[68-72] and their coworkers.

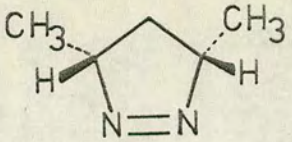
Crawford and coworkers[58] tend to favour a diradical mechanism for some simple pyrazolines (XLIII)-(XLVII). They studied the kinetics of decomposition of these compounds, and the regular decrease in activation energy as each additional methyl group is placed on the nitrogen-bearing carbon atoms, led them to suggest that both carbon-nitrogen bonds were being ruptured in the transition state. At the same time, these workers studied the/...



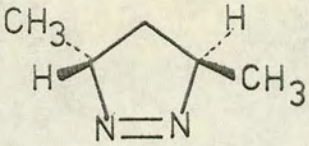
(XLIII)



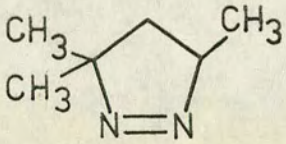
(XLIV)



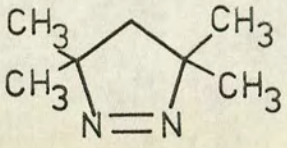
(XLVa)



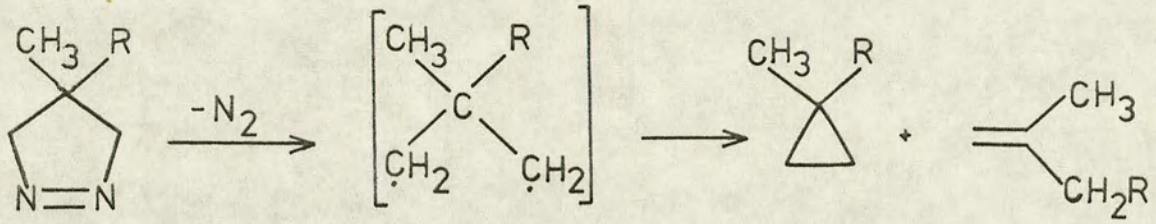
(XLVb)



(XLVI)



(XLVII)



(XLVIII) (XLIX)

a) 52% 48%

b) 66% 34%

(L) (LI)

a) R = H

b) R = D

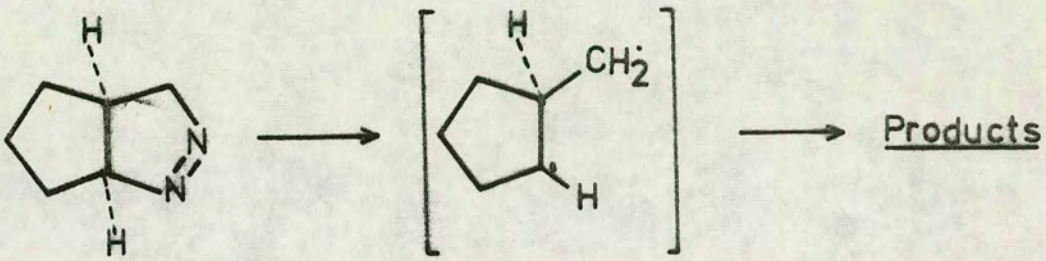
Scheme (14)

the decomposition of (XLVIII) (a) and (b) while the rate determining step remains unchanged on deuterium substitution at C_4, the product proportions have changed markedly. Crawford argued that this was consistent with the existence of the intermediate diradical (XLIX) and that the product-determining step was then that of hydrogen migration versus ring-closure giving (LI) and (L) respectively (scheme (14)).

In their study of the decomposition of 3,5-diphenyl-1-pyrazoline, Overberger and Anselme[64] also came to the conclusion that a diradical mechanism holds, but they did not investigate whether elimination of nitrogen was stepwise or concerted. The decomposition was stereospecific and led to trans-1,2-diphenylcyclopropane, both thermally and photochemically. ESR studies of the photolysis showed the presence of a free radical but no evidence for a triplet state. Overberger then suggested that due to their close proximity, the two radical sites coupled to form the cyclopropane before rotations about carbon-carbon bonds could occur to scramble the configuration of the product. The actual structure of such intermediate diradicals is still a matter of much controversy[73].

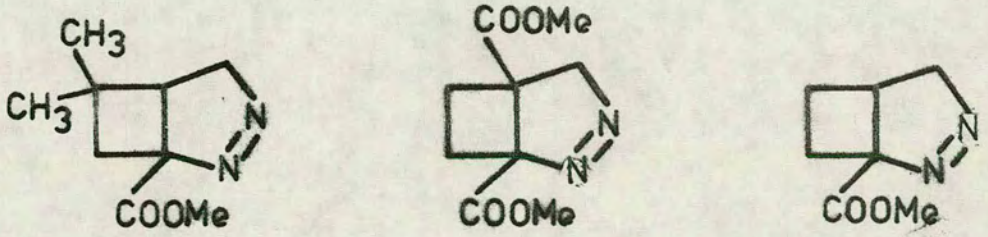
Several bicyclic pyrazolines such as (LII) react in a similar manner to simple monocyclic pyrazolines[68], presumably/...

presumably via the diradical (LIII):



(LII) (LIII)

However, data for the case of some related compounds containing a four-membered ring fused onto the pyrazoline ring are confusing.

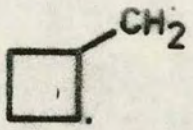


(LIV) (LV) (LVI)

Thus, (LIV) has been reported[74] to give typical bicyclopentane and olefin products although on photolysis, it was reported to form a "complex product mixture".

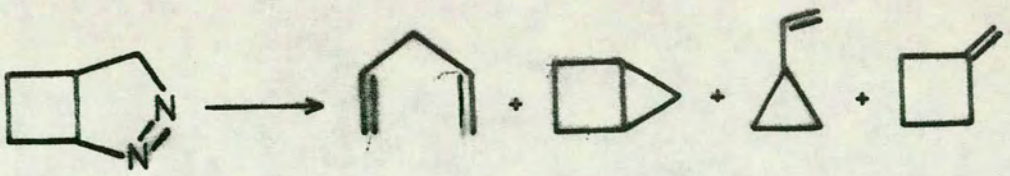
Another/...

Another system, (LV) decomposed to both bicyclopentane and 1,4-pentadiene products on irradiation, no thermal decomposition being reported[75]. Compound (LVI) produced 1-carbomethoxybicyclo-[2,1,0]-pentane and five other unidentified products when heated.[76] Furthermore, addition of carbenes and carbenoids to substituted cyclobutenes, which might directly generate diradicals of general structure (LVII) has been reported to give dienes, bicyclopentanes and vinylcyclopropanes as well as other products[77,78].

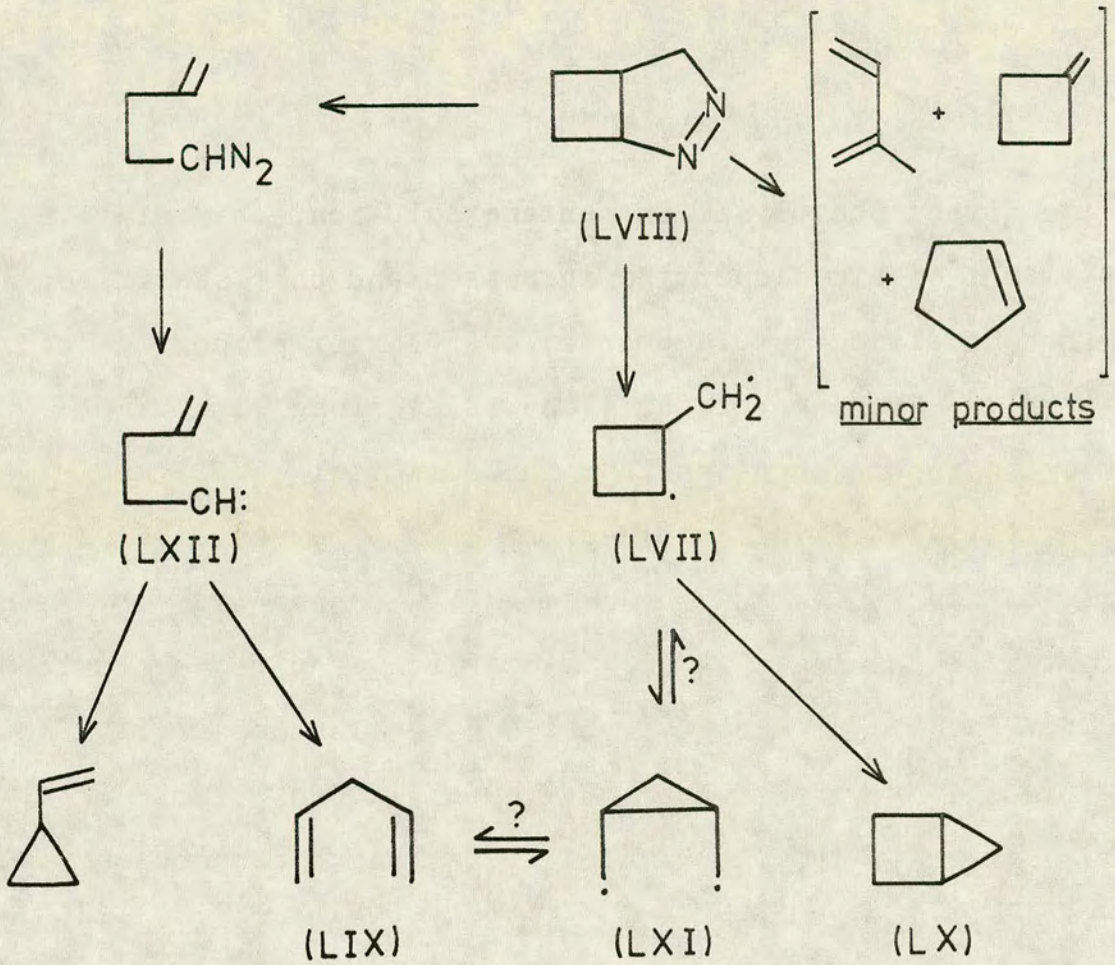


(LVII)

In order to clarify this confusion, Bergman[69] and co-workers undertook a study of the parent compound (LVIII) which gave a mixture of six products when thermolysed in the gas phase:



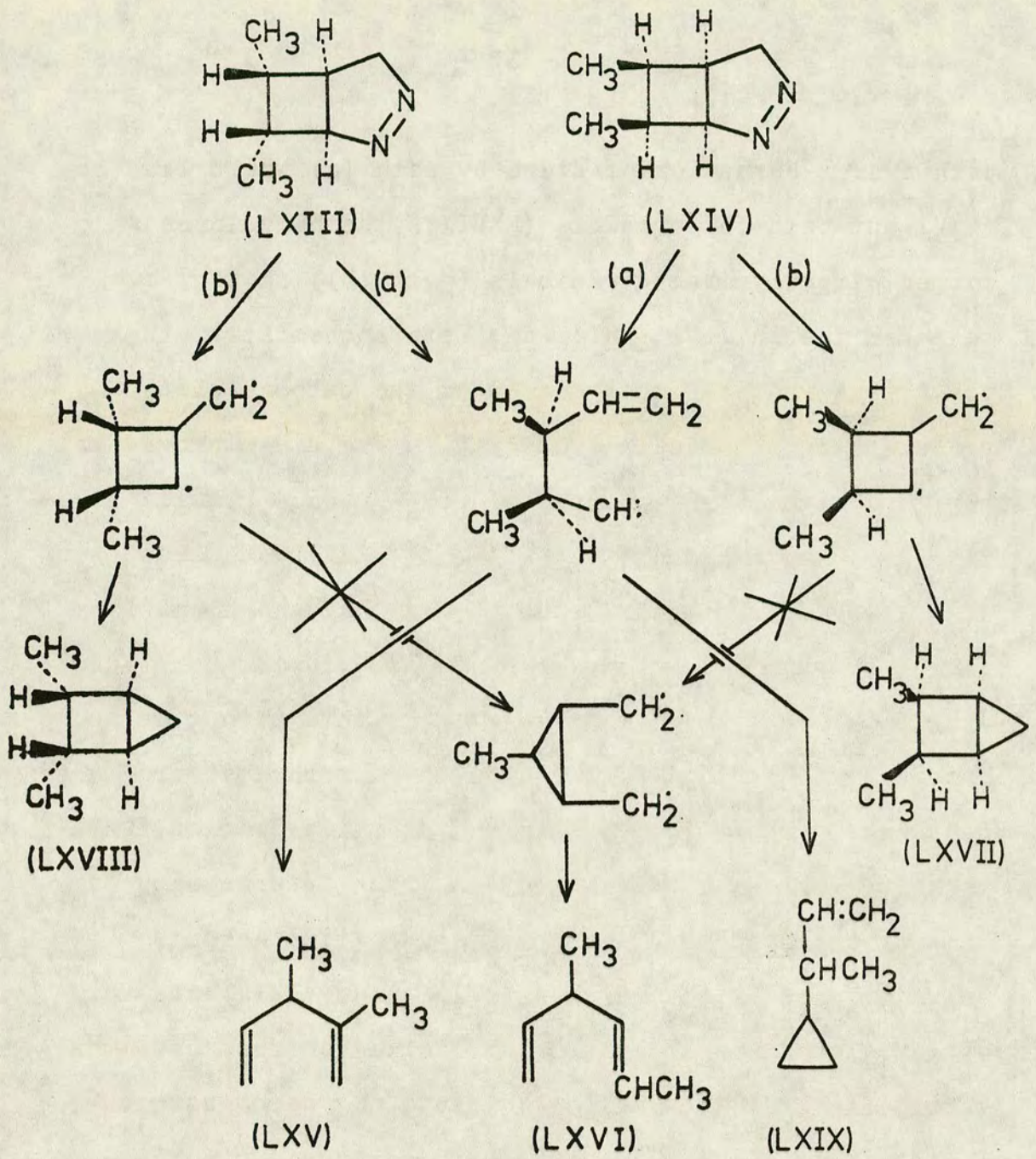
(LVIII)



Scheme (15)

On direct photolysis in pentane solution, the relative amount of bicyclopentane increased and photosensitised decomposition resulted in an even larger proportion of (LX). Presence of the diene (LIX) along with vinylcyclopropane suggests that the diradical (LVII), a potential initial intermediate may be in equilibrium with the isomeric diradical (LXI), (scheme (15)). Among other mechanistic alternatives, such as direct formation of vinylcyclopropane from (LVII), is the possibility that (LVIII) may first undergo a reverse 1,3-dipolar cycloaddition to give the diazocompound which decomposes via the carbene (LXII) to 1,4-pentadiene and vinylcyclopropane. To investigate this possibility, Bergman examined the products from the carbene (LXII) prepared from an independent source. This did in fact lead to 1,4-pentadiene (LIX) and vinylcyclopropane with no bicyclopentane. In other words, Bergman proposed that bicyclopyrazolines of type (LVIII) underwent thermolysis by a dual pathway in which there were two discrete intermediates giving rise to different products (scheme (15)).

To test for these competitive carbene and diradical mechanisms, Bergman[70] also studied the thermal decomposition of the doubly-labelled systems (LXIII) and (LXIV). As outlined in scheme (16), the stereochemistry and double-position labelling in these compounds are capable of distinguishing between the carbene and diradical pathways/...



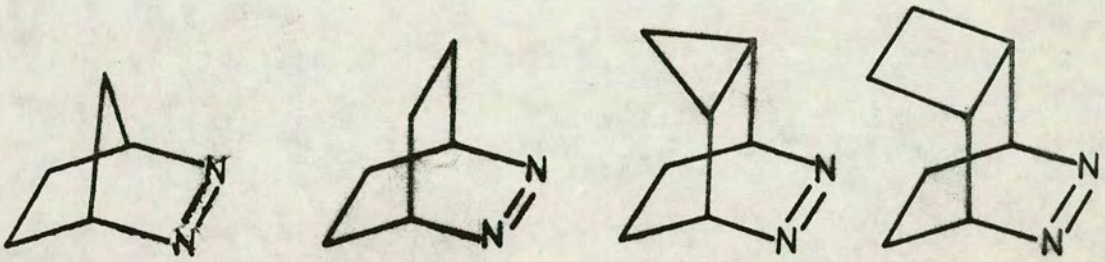
Starting Material	Conditions	Products % LXVIII	LXVII	LXV	LXIX
LXIII	gas phase 278°	13	<1	57	23
LXIV	" " "	<1	10	53	28

Scheme (16)

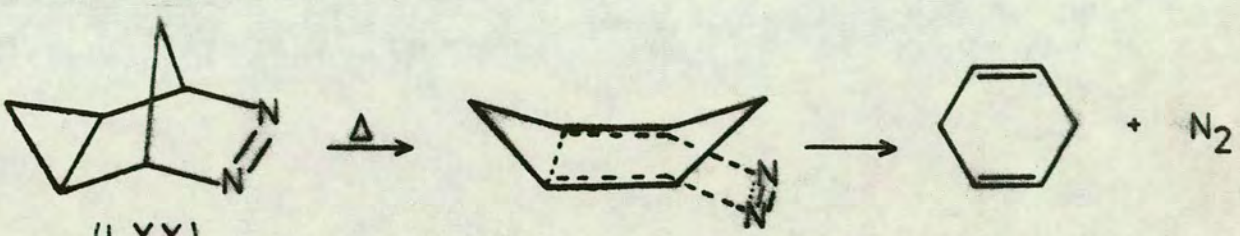
pathways. Formation of diene by path (a) would lead to (LXV) but path (b) predicts (LXVI); the bicyclopentanes formed directly from diradicals (path (b)) should have retained the initial syn or anti stereochemistry of their precursors whereas intervention of the carbene should produce stereochemical scrambling. The diene proved to be (LXV) with less than 0.1% of (LXVI) while (LXIII) gave rise to less than 1% of (LXVII) and (LXIV) gave less than 1% of (LXVIII). These results show that the diene is formed by path (a), the carbenic route, to the complete exclusion of path (b), but rigorously rule it out as an intermediate in the formation of the dimethylbicyclopentanes. Formation of the C-H insertion product (LXIX) constitutes additional evidence for the intermediacy of the carbene, and the fact that the relative amounts of (LXV) and (LXIX) formed from (LXIII) and (LXIV) are very similar is consistent with their formation from a common intermediate. Thus, at 278°, the major decomposition route is via the carbene and the minor route via the diradical pathway. As the temperature is raised, however, the percentage of carbene-type products decreases while diradical products increase in yield. This reaction provides the first evidence derived from product studies for a one-bond scission mechanism in the thermal and photochemical decomposition of cyclic azocompounds.

Many/...

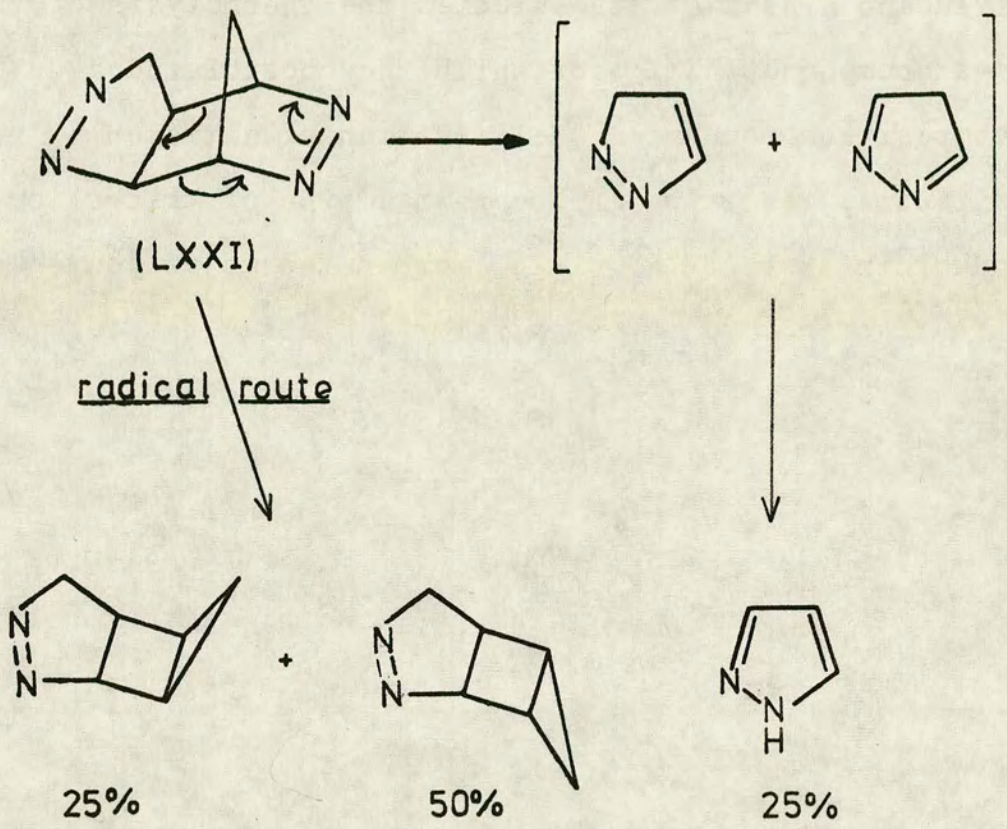
Many six-membered cyclic azocompounds have also been studied[79-83] with respect to their thermal and photochemical decomposition. Prominent among these are the decompositions of bicyclic and tricyclic ring systems such as the following:



In each case, diradical mechanism have been postulated and also it has been suggested that the intermediates are formed in a two-bond scission process. However, several examples of concerted mechanisms in the decomposition of this type of molecule are known. For example, Allred and coworkers[84] have shown that <u>exo</u>-6,7-diazatricyclo-[3,2,1,0]-6-octene (LXX) thermally eliminates nitrogen in a concerted manner which is symmetry-allowed:



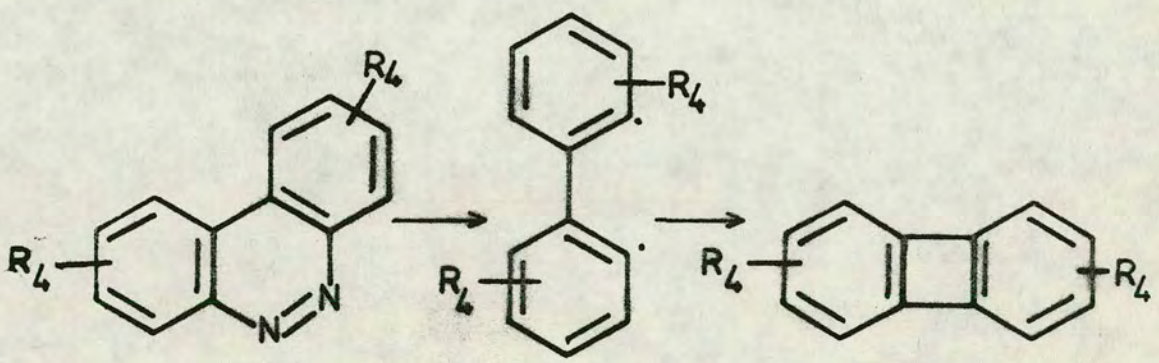
(LXX)



Scheme (17)

Allred and Hinshaw[85] also studied the thermolysis of the bis-azocompound (LXXI) for which they postulated a dual decomposition mechanism: elimination of nitrogen to form a diradical resulting in the normal type of tricyclic product in overall 75% yield, formed the major route, while the minor route was a reverse Diels-Alder reaction leading to pyrazole (25%) as the final product. (See scheme (17)).

A rather unusual nitrogen-elimination was reported by McBride[86] in 1972. This was the thermal extrusion of nitrogen from benzo-[c]-cinnoline and its perchloro-analogue:



a) R = H 870°/0.2 torr 42%

b) R = Cl 700°/0.2 torr 80%

McBride postulated a diradical mechanism rather than fragmentation to benzyne and recombination.

Until recently, there were few reports dealing with the decomposition/...

decomposition of seven and eight membered cyclic azo-compounds apart from two isolated reports by Overberger and his coworkers[63,87]. In both of these diradical mechanisms were postulated.

The work to be described in Part I of this Thesis concerns the thermal and photochemical decompositions of the 1,2-benzodiazepines of general structure (XVII) which have previously been prepared in this laboratory.

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Gas Phase Pyrolysis of 9-Cyclopentylidene-fluorene over Alumina 94

Attempted acid-catalysed isomerisation of 9-cyclopentylidinefluorene 95

Attempted base-catalysed isomerisation of 9-cyclopentylidenefluorene 95

Reaction of the product mixture, from the gas phase pyrolysis of 1,2,3,3a-tetrahydro-10-phenylbenzo-[c]-cyclopenta-[f]-1,2-diazepine with acid and with base 95

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Symbols and Abbreviations

The abbreviations used in this Thesis are those in common usage. In addition, the following symbols are used:

J	spin-spin coupling constant
m	multiplet
bs	broad singlet
sh	shoulder
m/e	mass/charge ratio
R_f	ratio of distance moved by substance to distance moved by solvent front
CIDNP	Chemically Induced Dynamic Nuclear Polarisation
HSLC	High Speed Liquid Chromatography
GLC	Gas Liquid Chromatography
GLC-MS	Gas Liquid Chromatography coupled to high resolution Mass Spectrometry

Instrumentation and Techniques

Gas Liquid Chromatography: All analytical investigations were carried out using a Pye Series 104 chromatograph with a flame ionisation detector, using 4mm internal diameter packed columns of length 1.5m. In all cases, the carrier gas was nitrogen, flow rates being as recommended by the manufacturers. The following stationary phases, supported on 100-200 mesh celite or silocel were employed: neopentylglycol succinate (NPGS), silicone elastomer (SE 30, SE 52), polyethyleneglycol adipate (PEGA) and silicone oil (OV1).

High Speed Liquid Chromatography was carried out on a Du Pont model 820 liquid chromatograph operated by Dr. J.N. Done. Columns and operating conditions are reported in the experimental kinetics section.

Column Chromatography: Alumina was Spence and Sons grade H, 100-200 mesh (Brockmann activity = I). For dry column chromatography,[88] this alumina was treated with the required amount of water to reduce the Brockmann activity to III or IV. Nylon tubing was supplied by Walter Coles and Co. Ltd., London.

Thin Layer Chromatography: Chromatograms were obtained on 0.33mm or 1.0mm layers of alumina (Merck Aluminium Oxide 9) or silica gel (Merck Kieselgel G (type 60)).

Components/...

Components in the developed chromatogram were detected by their fluorescence in uv light or by their reaction with iodine.

Proton Magnetic Resonance Spectroscopy: Routine spectra were obtained on a Perkin-Elmer model R10 or Varian EM360 nuclear magnetic resonance spectrometer operating at a frequency of 60 M Hz. In addition, a Varian HA100 spectrometer, operated by Mrs. M.N. Groves and Mr. J.R.A. Miller, was used for decoupling and CIDNP experiments, or when high resolution was required. Chemical shifts are recorded as tau (τ) values in parts per million (ppm), tetramethylsilane (TMS) being the internal reference. Spectra were determined on 10-15% w/v solutions or as indicated. ^{13}C nuclear magnetic resonance spectra were obtained using a Varian XL100 spectrometer operated by Mr. A.S.F. Boyd.

Mass Spectrometry: Mass spectra were obtained using an Associated Electrical Industries MS902 spectrometer operated by Mr. D.J.A. Thomas, or using an Associated Electrical Industries MS20 spectrometer coupled to a Pye Series 104 gas chromatograph. In the latter case the carrier gas was helium and the flow rate was 40ml/min.

Infrared Spectroscopy: Liquid samples were examined as thin films and solid samples as nujol mulls, both on polished sodium chloride plates, using Perkin Elmer 337 and 157G grating spectrometers.

Elemental Analyses: Microanalyses were carried out by Mr. B. Clarke and Mr. J. Grunbaum, Chemistry Department, University of Edinburgh, or by the National Physical Laboratory.

Melting Points: The melting points of all new compounds were obtained on a Kofler hot-stage apparatus.

Gas Phase Pyrolysis Reactions were carried out in the apparatus described in the Discussion section of this Thesis. This apparatus was designed and built by Professor W.D. Crow,[89] of the Australian National University, while on a sabbatical year in this country.

Photochemical Reactions: A Hanovia 100 watt medium pressure mercury arc tube in a quartz envelope was surrounded by the reaction mixtures contained in a pyrex reaction vessel of appropriate capacity.

Preparation and Purification of Reagents, Solvents and Reference Compounds

"Super-dry" ethanol was prepared as described by Vogel[90] (method 1).

1,2-Dimethoxyethane (DME) was boiled under reflux over calcium hydride (BDH commercial grade) under dry, oxygen-free nitrogen for ten hours and allowed to stand over calcium hydride. This was then freshly-distilled from calcium/...

calcium hydride, under nitrogen, as required.

Cyclohexane was purified in the same manner as DME.

Benzene was purified in the same manner as DME.

Toluene, xylene, mesitylene, chlorobenzene, bromobenzene t-butylbenzene, dodecane and hexadecane were dried over phosphorus pentoxide, distilled and stored over sodium wire or activated molecular sieve as appropriate. Other common solvents and reagents were purified by standard procedures.

Petroleum refers to the fraction bp 40-60° unless otherwise stated.

All organic solutions were dried over anhydrous magnesium sulphate.

Butyllithium was the 15% solution in n-hexane as supplied by Koch-Light.

Preparation of Starting Materials

2-Ethylenedioxyethoxycarbonylcyclopentane

This compound was prepared by an adaptation of the method of Black, Buchanan and Jarvie.[91] 2-Ethoxycarbonylcyclopentanone (168g, 1.05 mole), ethylene glycol (113g, 1.80 mole), toluene-p-sulphonic acid (0.85g) and dry benzene (320 ml)/...

(320 ml) were heated under reflux, and the water formed in the reaction was removed using a Dean and Stark apparatus. After 13h, no more water was collected, and after cooling the reaction mixture, benzene (85ml) was added. The benzene solution was washed with 15% sodium carbonate solution (2 x 100ml) and then with water (2 x 100ml). After drying, the benzene solution was concentrated under reduced pressure to give a yellow oil, distillation of which afforded 2-ethylenedioxyethoxycarbonylcyclopentane (100g,48%), bp. 82°/0.1mm Hg as a colourless oil. Examination by glc (2% NPGS, 120°) showed that the product was pure.

IR (liquid): $1730cm^{-1}$, C=O

2-Diphenylmethylenecyclopentanone

Phenylmagnesium bromide was prepared by the addition of bromobenzene (52.0g, 0.33 mole) in ether (125ml) to magnesium turnings (8.5g, 0.35 mole) in ether (35ml) under dry nitrogen. After addition of all the bromobenzene solution, the mixture was heated under reflux for 20 minutes to complete the reaction. 2-Ethylenedioxyethoxycarbonylcyclopentane (35g, 0.165 mole) in ether (75ml) was added dropwise, with vigorous mechanical stirring, at a rate sufficient to maintain a gentle reflux. The mixture was heated under reflux with stirring/...

stirring for a further four hours. After cooling, a solution of ammonium chloride (75g) in water (200ml) was added to decompose the complex. The aqueous layer was washed with ether (2 x 100ml), and the ether extracts combined and evaporated under reduced pressure to afford a deep yellow oil. Hydrolysis and dehydration were carried out by heating the oil under reflux with a mixture of methanol (80ml), water (55ml) and concentrated hydrochloric acid (4ml) for 2.5h with vigorous stirring. Examination of the reaction mixture by glc (2% NPGS, 180°) showed that dehydration was complete. On cooling, a yellow solid separated. This was filtered off and the aqueous methanol evaporated under reduced pressure. Petroleum ether (50ml) was added to the residue, the mixture shaken and set aside at -6° for 48h at which time a further batch of yellow crystals was filtered off. Recrystallisation of the solid from ethanol afforded 2-diphenylmethylenecyclopentanone (12.0g, 30%), mp 113-115° (lit.,[25] 114-115°), as yellow needles.

IR Spectrum (Nujol): 1700cm^{-1}, C=O

NMR Spectrum ($CDCl_3$), 2.75τ, (m), 10H; 7.4τ, (t), 2H; 8.1τ, (q), 2H, 7.7τ, (m), 2H.

2-Diphenylmethylenecyclopentanone Toluene-p-sulphonylhydrazone

A solution of 2-diphenylmethylenecyclopentanone (5.0g, 0.02 mole) in ethanol (40ml) was added to a solution of/...

of toluene-p-sulphonylhydrazide (3.75g, 0.02 mole) in ethanol (40ml) containing conc. hydrochloric acid (0.3ml), both solutions being previously warmed to 50°. After stirring for a few minutes, the reaction mixture was set aside for 5h, when a buff precipitate was filtered off. Recrystallisation from an ethanol-benzene mixture afforded 2-diphenylmethylenecyclopentanone toluene-p-sulphonylhydrazone as colourless needles (6.68g, 80%) mp 166° (decomp.); (lit.,[25] 166° (decomp.))

IR Spectrum (Nujol): 3200cm^{-1}, N-H

Nmr Spectrum ($CDCl_3$): 2.85τ, (m), 14H; 7.3τ-8.5τ, (m), 9H.

Sodium salt of 2-Diphenylmethylenecyclopentanone Toluene-p- sulphonylhydrazone and its Cyclisation to 1,2,3,3a-Tetrahydro-10-phenylbenzo- [c] -cyclopenta- [f]-1,2-diazepine

Sodium (0.115g, 0.005 mole) was dissolved in dry ethanol (55ml) and 2-diphenylmethylenecyclopentanone toluene-p-sulphonylhydrazone (2.073g, 0.005 mole) was added. The mixture was stirred at room temperature in the dark for 0.5h. Initially, the tosylhydrazone dissolved, after which the sodium salt was precipitated. The ethanol was evaporated under reduced pressure, and the solid salt was dissolved in 1,2-dimethoxyethane (DME) (100ml), and the latter solvent evaporated under reduced pressure to/...

to remove the last traces of ethanol. The residue was vacuum-dried over phosphorus pentoxide for twelve hours after which dry DME (60ml) was added to dissolve it. The solution was heated under reflux under an atmosphere of dry nitrogen for 5h. TLC (silica, benzene) then showed a single product spot of R_f value identical to that of authentic benzodiazepine. The solution was filtered to remove the unwanted precipitate of sodium p-toluene-sulphinate and the filtrate evaporated under reduced pressure to afford an amorphous yellow solid which on re-crystallisation from ethanol proved to be 1,2,3,3a-tetra-hydro-10-phenylbenzo-[c]-cyclopenta-[f]-1,2-diazepine (0.844g, 80%), mp = 157-159° (lit.,[25] 159-160) as yellow needles.

NMR Spectrum ($CDCl_3$): 2.24τ, (m), 1H; 2.8τ, (m), 8H; 6.84τ, (m), 1H; 7.1τ-8.1τ, (m), 6H.

2-(Di-p-tolylmethylene)cyclopentanone

The Grignard reagent was prepared from p-bromotoluene (26.0g, 0.15 mole) and magnesium turnings (4.26g, 0.18 mole) in dry ether (100ml). After addition of all the bromocompound, the mixture was heated under reflux, with stirring for 0.5h. When cool, 2-ethylenedioxyethoxy-carbonylcyclopentane (15.0g, 0.075 mole) in dry ether (40ml)/...

(40ml) was added dropwise, with mechanical stirring. The rate of addition was just sufficient to maintain a gentle reflux. The mixture was heated under reflux for 6h then set aside overnight at room temperature. The complex was decomposed by the addition of a solution of ammonium chloride (40.0g) in water (200ml). After filtering off the excess magnesium, the organic layer was separated and the aqueous layer washed with ether (100ml). The ether extracts were combined and dried. The solvent was evaporated under reduced pressure to give a yellow oil. To this was added ethanol (80ml), water (55ml) and conc. hydrochloric acid (1ml), and the mixture was stirred vigorously and heated under reflux for 2h, then stirred at room temperature overnight. The precipitated yellow solid was filtered off and the mother liquor neutralised with saturated sodium bicarbonate solution. Extraction with chloroform (2 x 50ml) and evaporation of the solvent gave a yellow oil which was dissolved in benzene (35ml) and petroleum ether (10ml) was added. This was set aside at -6^{o} overnight when a second batch of yellow crystals was filtered off. Recrystallisation from ethanol yielded 2-(di-p-tolylmethylene)cyclopentanone (7.04g, 34%) mp = 140-143° (lit.,[25] 142-143°) as pale yellow plates.

IR Spectrum (Nujol): 1700cm^{-1}, C=O

NMR Spectrum ($CDCl_3$): 2.9τ, (m), 8H; 7.2τ, (t), 2H; 7.45τ-8.4τ, (m), 10H.

2-(Di-p-tolylmethylene)cyclopentanone Toluene-p-sulphonylhydrazone

A solution of 2-(di-p-tolylmethylene)cyclopentanone (5.5g, 0.02 mole) in ethanol (60ml) was added to a solution of toluene-p-sulphonylhydrazide (3.7g, 0.02 mole) in ethanol (30ml) containing conc. hydrochloric acid (0.2ml), both solutions having been warmed to 50° before mixing. The mixture was set aside for 8h when the colourless precipitate was filtered off. Recrystallisation from a benzene: 60-80 petroleum mixture (1:1) gave 2-(di-p-tolylmethylene) cyclopentanone tosylhydrazone as colourless needles (6.1g, 70%) mp = 176° (decomp.) (lit.,[25] mp = 176° (decomp.)).

IR Spectrum (Nujol): $3250cm^{-1}$, N-H

NMR Spectrum ($CDCl_3$): 2.9τ, (m), 12H; 7.2τ-8.4τ, (m), 15H.

Sodium Salt of 2-(Di-p-tolylmethylene)cyclopentanone Toluene-p-sulphonylhydrazone and its Cyclisation to 1,2,3,3a-Tetrahydro-7-methyl-10-(p-tolyl)benzo-[c]-cyclopenta-[f]-1,2-diazepine

Sodium (0.156g, 0.0068 mole) was dissolved in dry ethanol (110ml) and 2-(di-p-tolylmethylene)cyclopentanone tosylhydrazone (3.16g, 0.0071 mole) was added. The mixture was stirred in the dark at room temperature for 1h, after which time the sodium salt had precipitated out. The

ethanol was evaporated under reduced pressure and the solid residue dissolved in dry DME (100ml). This solvent was evaporated under reduced pressure to remove the last traces of ethanol. The residual solid was vacuum-dried over phosphorus pentoxide for 16h after which dry DME (125ml) was added to dissolve it. This solution was heated under reflux under an atmosphere of dry nitrogen for 4h. TLC (silica-benzene) then showed a single product spot of identical R_f value to that of authentic benzodiazepine. The solution was filtered to remove the unwanted precipitate of sodium-p-toluenesulphinate, and the filtrate was evaporated under reduced pressure to afford an amorphous yellow solid. Recrystallisation of this gave 1,2,3,3a-tetrahydro-7-methyl-10-(p-tolyl)benzo-[c]-cyclopenta-[f]-1,2-diazepine (1.13g, 67%) mp = 175-176° (lit.,[25] 177-178°) as yellow needles.

NMR Spectrum ($CDCl_3$): 2.44τ, (m), 1H; 2.95τ, (m), 6H; 6.88τ, (m), 1H; 7.2 - 8.06τ, (m), 12H

Gas Phase Pyrolysis of 1,2,3,3a-Tetrahydro-10-phenylbenzo-[c]-cyclopenta-[f]-1,2-diazepine

(i) At 400°

The benzodiazepine (0.513g, 0.002 mole) was placed in the preheater of the pyrolysis apparatus and a vacuum of 0.005/...

0.005mm Hg applied. The furnace temperature was adjusted to and equilibrated at 400° after which the preheater temperature was set at 150°. This allowed the reactant to diffuse slowly through the furnace, the products being collected in a liquid nitrogen trap. After 16h, the product trap was washed out with acetone, and the solvent evaporated under reduced pressure to afford a yellow oil (0.450g, 98.3%) constituting the volatile products. GLC analysis (2½% OV1, 190°) showed a mixture of four compounds while glc-coupled to mass spectrometry showed each of these to have a molecular ion of 232^+.

The mixed pyrolysis products (0.265g) were dissolved in ethanol (35ml) containing conc. hydrochloric acid (0.1ml) and 10% palladium charcoal powder (200mg) added. The mixture was hydrogenated at four atmospheres for 1h. Examination by glc (2½% OV1, 202°) showed the presence of only two products which were separated by column chromatography on alumina (4ft x ½" column), eluting with petroleum.

Fraction 1: 1-phenyl-1H-cyclopenta-[b]-indane (79mg, 30%)

Found: C 92.2%, H 7.7%; $C_{18}H_{18}$ requires C 92.3%, H 7.7%)

IR Spectrum (Liq. film): 3060, 3020cm^{-1}, aromatic CH; 2940, 2860cm^{-1}, saturated C-H

NMR Spectrum (CCl_4): 2.9τ, (m), 9H; 5.42τ, d, (J=8cps) 1H; 6.38τ, t of d (J=8cps, J'=4 cps), 1H 7.01τ, q (J=8cps), 1H; 7.6-9.02τ, (m), 6H.

Mass Spectrum: See Appendix I.6

Mass Measurement: Found M^+ = 234.140191
$C_{18}H_{18}$ M^+ = 234.140844
Error < 1ppm

Fraction 2: 9-Cyclopentylfluorene (83mg, 31%) mp = 60-61° (colourless needles from ethanol) (lit.,[91] 60-62.4°)

Found: C 92.2% H 7.7% $C_{18}H_{18}$ requires C 92.3% H 7.7%)

NMR Spectrum (CCl_4): 2.37τ, (m), 2H; 2.58τ, (m), 2H; 2.80τ, (m), 4H; 6.08τ, (d) (J= 5cps), 1H; 7.66τ, (m), 1H; 8.1-9τ, (m), 8H

Mass Spectrum: See Appendix I.6

Mass Measurement: Found: M^+ = 234.141807
$C_{18}H_{18}$ M^+ = 234.140844
Error < 1ppm

(ii) Pyrolysis at 200°

The benzodiazepine (80mg, 0.31m mole) was pyrolysed in the gas phase at 200° with a preheater temperature of 150°. The pressure was 0.0001mm Hg. After 16h the product was collected in acetone solution, TLC (alumina, benzene) of which showed a single spot of the same R_f value as authentic diazepine. Evaporation of the solvent under reduced pressure afforded 1,2,3,3a-tetrahydro-10-phenyl-benzo-[c]-cyclopenta-[f]- 1,2 -diazepine (mp 158-159°) in/...

in quantitative yield.

NMR Spectrum (CCl_4): 2.24τ, (m), 1H; 2.8τ, (m), 8H; 6.84τ, (m), 1H; 7.1-8.1τ, (m), 6H.

(iii) Pyrolysis at 300°

The benzodiazepine (50mg, 0.192m mole) was pyrolysed at 300° using an inlet temperature of 150° for 3h at a pressure of 0.0001mm Hg. TLC (alumina, benzene) showed a three component mixture corresponding in R_f values to unchanged benzodiazepine, hydrocarbon product and a third component lying between these two. HSLC showed three peaks due to a small amount of hydrocarbon, (55) and the benzodiazepine respectively, the latter products in the ratio 1:1.

(iv) Pyrolysis at 260°

The benzodiazepine (260mg, 1.154m mole) was pyrolysed at 260° in a glass-wool packed furnace using an inlet temperature of 150° and pressure of 0.0001mm Hg for 16h. The product oil was chromatographed on alumina (12" x ½") using benzene as eluting solvent.

Fraction 1: brown oil which, on standing under petroleum at -6°, gave a white crystalline solid. Recrystallisation from ethanol afforded 3-phenyl-3-(cyclopent-1-enyl)-3H-indazole (88mg, 34% as colourless needles mp 66-67°).

Found: C 82.9% H 6.4% N 10.9%
$C_{18}H_{16}N_2$ requires C 83.1% H 6.1% N 10.8%)

^{1}HNMR Spectrum (CCl_4): 2.0τ, (m), (1H, aromatic); 2.7τ, (m), (8H, aromatic); 4.4τ, (bs), (1H olefinic); 7.68τ, (triplet), (4H, aliphatic); 8.14τ, (q), (2H aliphatic).

^{13}C NMR Spectrum: See Appendix I.9

Mass Spectrum: See Appendix I.10

Fraction 2: 1,2,3,3a-Tetrahydro-10-phenylbenzo-[c]-cyclo-penta-[f]- 1,2 -diazepine (83mg, 32%) mp = 158-159^o (lit.,[25] 159^o)

NMR Spectrum (CCl_4): 2.24τ, (m), 1H; 2.8τ, (m), 8H; 6.84τ, (m), 1H; 7.1-8.1τ, (m), 6H.

Gas Phase Pyrolysis of 1,2,3,3a-Tetrahydro-7-methyl-10-(p-tolyl)-benzo-[c]-cyclopenta-[f]-1,2-diazepine

(i) Pyrolysis at 400^o

The benzodiazepine (500mg, 1.74m mole) was pyrolised at 400^o using a preheater temperature of 170^o and a pressure of 0.01mm Hg. After 16h, the products were collected in the usual manner, yield being quantitative. GLC and GLC-MS (2½% OV1, 210^o) showed the product to be a mixture of four compounds of molecular weight 260.

The/...

The total yield of pyrolysate (452mg, quant.) was dissolved in ethanol (50ml) containing conc. hydrochloric acid (0.1ml) and 10% palladium charcoal powder (310mg) was added. This mixture was hydrogenated at four atmospheres pressure, reaction time being one hour. Examination of the product solution by glc (2½% OV1, 210°) showed two products in the ratio 1:1-37. The solution was filtered through celite and the residue vacuum-dried, leaving a colourless oil (367mg, 80%) The two components of the mixture were separated by column chromatography on alumina (4.5ft x ¾") eluting with petroleum.

Fraction 1: 1-(p-tolyl)-5-methylcyclopenta-[b]-indane (123mg, 27%), a colourless oil, bp 110°/0.1mm Hg

Found: C 91.7%, H 8.5%; $C_{20}H_{22}$ requires C 91.6%, H 8.4%).

NMR Spectrum (CCl_4): 3.02τ, (s), 4H; 3.09τ, (s), 1H; 3.17τ, (s), 2H; 5.50τ, (d, J= 8cps), 1H; 6.44τ, (m), 1H; 7.04τ, (m), 1H; 7.70τ, (s), 6H; 7.72τ-9.06τ, (m), 6H.

Mass Spectrum: See Appendix I.7

Mass Measurement: Found: M^+ = 262.172979
$C_{20}H_{22}$ requires M^+ = 262.172142
(Error <1ppm)

Fraction 2: 3,6-Dimethyl-9-cyclopentylfluorene (119mg, 26%) as colourless needles mp 60.5-62° from ethanol

Found: C 91.6%, H 8.3%; $C_{20}H_{22}$ requires C 91.6%, H 8.4%)

NMR Spectrum (CCl_4): 2.59τ, (bs), 2H; 2.69τ, (d, J=9cps), 2H; 3.05τ, (bd, J= 9cps), 2H; 6.16τ, (d J=8cps), 1H; 7.61τ, (s), 6H; 7.61τ, (m), 1H; 8.12-9.08τ, (m), 8H

Mass Spectrum: See Appendix I.7

Mass Measurement: Found: M^+ = 262.171892 $C_{20}H_{22}$ requires M^+ = 262.172142 (Error <1ppm)

(ii) Pyrolysis at 260°

The benzodiazepine (288mg, 1m mole) was pyrolysed at 260° in a glass-wool packed furnace using a preheater temperature of 170° and a pressure of 0.0001mm Hg for 16h. HSLC analysis of the product mixture showed two peaks which were assigned tentatively to indazole and benzodiazepine ring systems. Due to lack of time, this experiment was not pursued further.

Solution Phase Decomposition of Benzodiazepines

General Method: The required weight of benzodiazepine was dissolved in dried, degassed solvent and heated under reflux under an atmosphere of dry, oxygen-free nitrogen. Reactions were carried out in the dark until TLC (alumina; benzene/...

benzene/petroleum, 50/50) showed that no more diazepine was left. In all cases, the product solutions were examined by glc (2½% OV1, 190-220° or 1% SE30, 170-190°) and glc-mass spectrometry.

The solvent was evaporated under reduced pressure, the residue dissolved in acidified ethanol and palladium charcoal added. The mixture was hydrogenated at four atmospheres pressure on a Parr Hydrogenator. The hydrogenated products were identified by their glc retention times and glc-mass spectra yields were obtained by glc.

Solution Phase Thermolysis of 1,2,3,3a-Tetrahydro-10-phenylbenzo-[c]-cyclopenta-[f]-1,2-diazepine

(i) Decomposition in Dodecane (reflux temperature 216°)

Compound (5a) (1.15g, 0.0044 mole) was dissolved in dodecane (150ml) and the solution was heated under reflux for 45 min. The solvent was evaporated under reduced pressure and the residue was distilled to afford the mixed products (0.775g, 76%) bp 125-130°/0.1mm Hg. The mixture (50mg, 0.195m mole) was dissolved in acidified ethanol (30ml). The solution was hydrogenated over 10% palladium charcoal powder (70mg) in the usual way. Examination of the product solution by glc and glc/ms showed a mixture of (diphenylmethyl)cyclopentane (38%) 1-phenyl-1H-cyclopenta-[b]-indane (31%) and 9-cyclopentyl-fluorene (10%). Yield of hydrocarbon product on distillation was 35mg (79%).

(ii) Decomposition in Mesitylene (reflux temperature 165°)

Compound (5a) (50mg, 0.195m mole) was dissolved in mesitylene (30ml) and boiled under reflux overnight. The solvent was evaporated under reduced pressure and the residue dissolved in acidified ethanol (40ml). This solution was hydrogenated over 10% palladium charcoal powder (50mg) in the normal way. Examination of the product solution by glc and glc-ms showed a mixture of (diphenylmethyl)cyclopentane (13%), 1-phenyl-1H-cyclopenta-[b]-indane (54%) and 9-cyclopentylfluorene (8%). The total yield of hydrocarbon product on distillation was 34mg (75%).

(iii) Decomposition in t-Butylbenzene (reflux temperature 160°)

The benzodiazepine (100mg, 0.39m mole) was dissolved in t-butylbenzene (50ml) and thermolysed at the reflux temperature (160°) as described in the general method, reaction time being 24h. The solvent was evaporated under reduced pressure and the residue dissolved in acidified ethanol (50ml). This solution was hydrogenated over 10% palladium charcoal (63mg) in the usual way. Filtration through celite and evaporation of the solvent followed by distillation of the residue gave (89mg 64%) of volatile product. GLC and glc-ms identified the products as (diphenylmethyl)cyclopentane (23%), 1-phenyl-1H-cyclopenta-[b]-indane (39%) and 9-cyclopentylfluorene (2%).

(iv) Decomposition in Xylene (reflux temperature 134°)

The benzodiazepine (800mg, 3.12m mole) was dissolved in xylene (175ml) and thermolysed in the usual way for eight days. The solvent was evaporated under reduced pressure and the residue was vacuum-distilled to give a yellow oil (3.65g) bp 125-140°/0.1mm Hg. 1.7g of this mixture was dissolved in acidified ethanol (50ml) and hydrogenated over 10% palladium charcoal powder (500mg) in the normal manner. After filtration from the catalyst and evaporation of the solvent, the product was chromatographed on an alumina dry-column (3ft x ½") eluting with n-pentane to remove the polymeric material. The hydrocarbon band was vacuum-distilled to give the hydrocarbon product (190mg, 46%). Examination of the product by glc and glc/ms showed the products to be (diphenylmethyl)cyclopentane (8%), 1-phenyl-1H-cyclopenta-[b]-indane (36%) and 9-cyclopentyl-fluorene (2%).

(v) Decomposition in Chlorobenzene (reflux temperature 132°)

Benzodiazepine (50mg, 0.195m mole) was dissolved in chlorobenzene (30ml) and thermolysed at the reflux temperature (132°) for seven days. The solvent was evaporated under reduced pressure, and the residue dissolved in acidified ethanol (30ml). The solution was hydrogenated over/...

over 10% palladium charcoal powder (60mg) and hydrogenated in the normal manner. Filtration, evaporation of the solvent and vacuum-distillation of the residue afforded the volatile products (35.3mg, 78%). The products were identified by glc and glc-ms (1% SE30, 168°) and yields obtained by glc as (diphenylmethyl)cyclopentane (36%) and 1-phenyl-1H-cyclopenta-[b]-indane (42%).

(vi) Decomposition in Toluene (reflux temperature 111°)

Benzodiazepine (100mg, 0.39m mole) was dissolved in toluene (50ml) and thermolysed at the reflux temperature (111°) for 16 days. The solvent was evaporated under reduced pressure and the residue dissolved in acidified ethanol (50ml), 10% palladium charcoal powder (60mg) added and the mixture hydrogenated in the usual way. Filtration, evaporation of the solvent and vacuum-distillation of the residue gave the usual oily product mixture. Examination of this by glc and glc-ms showed the products to be (diphenylmethyl) cyclopentane (21%) and 1-phenyl-1H-cyclopenta-[b]-indane (59%).

(vii) Decomposition in Toluene-d_8 (reflux temperature 111°)

Duplicate samples of the diazepine (10mg, 0.039m mole) were dissolved in dry, deoxygenated toluene (2ml) and toluene-d_8 (2ml)/...

(2ml) and these were heated under reflux under an atmosphere of dry oxygen-free nitrogen in identical conditions for three weeks. On cooling, each reaction mixture was rapidly passed through a small dry column ($2\frac{1}{2}$" x $\frac{5}{8}$") of grade IV alumina, and the products washed through with petroleum (ca. 5ml). Identical glc traces were obtained for each solution (1% SE30, 181°). The solutions were then examined by glc-ms at several temperatures, spectra being obtained for 3-diphenylmethylenecyclopent-1-ene in each case. The ratio $(^{M+1}/M) \times 100$ was calculated for each sample pair at each temperature. (M = parent peak). There proved to be no difference in this ratio for the toluene and toluene-d_8 reactions.

(viii) Decomposition in Benzene (reflux temperature 78°)

The benzodiazepine (100mg, 0.39m mole) was dissolved in benzene (30ml) and thermolysed at the reflux temperature (78°) for 30 days. The solvent was evaporated under reduced pressure and the residue was chromatographed on alumina (9" x $\frac{1}{4}$").

Fraction 1: petrol, 9mg, brown oil. GLC showed this to be mainly high molecular weight material.

Fraction 2: 40% benzene:petroleum, yellow crystalline solid 77mg (77%). TLC (alumina, benzene) gave a single spot of R_f value identical with that of authentic benzodiazepine. NMR confirmed identity of the product as unreacted diazepine.

NMR Spectrum (CCl_4): 2.24τ, (m), 1H; 2.8τ, (m), 8H; 6.84τ, (m), 1H; 7.1-8.1τ, (m), 6H.

Solution Phase Thermolysis of 1,2,3,3a-Tetrahydro-7-methyl-10-(p-tolyl)benzo-[c]-cyclopenta-[f]-1,2-diazepine

i) Decomposition in Dodecane (reflux temperature 216°)

The benzodiazepine (50mg, 0.175m mole) was dissolved in dodecane (50ml) and thermolysed as outlined in the general method overnight. The solvent was evaporated under reduced pressure and the residue dissolved in acidified ethanol (50ml). The resulting solution was hydrogenated over 10% palladium charcoal powder (50mg) in the normal way. Examination of the product solution by glc (1% SE30, 168°) and glc-ms showed a main product of di-(p-tolyl-methyl)cyclopentane with traces of 1-p-tolyl-5-methyl-1H-cyclopenta-[b]-indane and 3,6-dimethyl-9-cyclopentyl-fluorene. Distillation of the residue after evaporation of the ethanol afforded di-(p-tolylmethyl)cyclopentane (42mg, 86%) as a colourless oil bp 110°/0.001mm Hg.

NMR Spectrum (CCl_4): 3.0τ, (m), 8H; 6.58τ (d), (J=11cps), 1H; 7.4τ, (m), 1H; 7.74τ, (s), 6H; 8.2τ-9.1τ, (m), 8H.

ii) Decomposition in t-Butylbenzene (reflux temperature 160°)

The benzodiazepine (50mg, 0.175m mole) was dissolved in t-butylbenzene and thermolysed by the general method for 17h. The solvent was evaporated under reduced pressure and the residue taken up in acidified ethanol (50ml). The resulting solution was hydrogenated in the usual manner over 10% palladium charcoal powder (50mg). Examination of the solution by glc and glc-ms (1% SE30, 170°) showed a mixture of (di-tolylmethyl)cyclopentane, 1-p-tolyl-5-methyl-1H-cyclopenta-[b]-indane and 3,6-dimethyl-9-cyclopentylfluorene in yields of 41%, 40% and 7% respectively.

iii) Decomposition in Xylene (reflux temperature 134°)

The benzodiazepine (800mg, 2.8m mole) was dissolved in xylene (75ml) and thermolysed for 15 days in the usual way. The solution was examined by glc to show one major product. The solvent was evaporated under reduced pressure, and the residue was chromatographed on an alumina dry column (20" x 1") using cyclohexane as eluting solvent. The fast-running hydrocarbon band was extracted into ether (2 x 50ml) and the ether evaporated to afford 3-di-(p-tolyl)methylenecyclopentene (391mg, 55%).

NMR Spectrum (CCl_4): 3.00τ, (m), 8H; 3.04τ, (m), 1H; 3.96τ, (m), 1H; 7.72τ, (s), 6H; 7.2-7.9τ, (m), 4H.

3-Di-(p-tolylmethylene)cyclopentene (352mg, 1.7m mole) was dissolved in ethanol (100ml) and 10% palladium charcoal powder (300mg) added. This was hydrogenated in the usual way. The solution was filtered, the solvent evaporated, and the residue vacuum-distilled to afford di-(p-tolylmethyl)cyclopentane (350mg, quantitative) as a colourless oil bp 100°/0.01mm Hg.

NMR Spectrum (CCl_4): 3.01τ (m), 8H; 6.6τ, (d, J= 11cps), 1H; 7.76τ, (s), 6H; 7.74τ, (m), 1H; 8.2-9.1τ, (m), 8H

iv) Decomposition in Chlorobenzene (reflux temperature 132°)

The benzodiazepine (50mg, 0.175m mole) was dissolved in chlorobenzene (30ml) and thermolysed by the general method for seven days. The solvent was evaporated under reduced pressure and the residue (45mg, 90%) was dissolved in acidified ethanol (30ml) and hydrogenated over 10% palladium charcoal powder (70mg) in the usual manner. Examination of the product solution by glc and glc-ms (1% SE30, 170°) showed the presence of (di-p-tolylmethyl)cyclopentane (62.5%) and 1-p-tolyl-5methyl-1H-cyclopenta-[b]-indane (31.5%).

v) Decomposition in Toluene (reflux temperature 111°)

The benzodiazepine (100mg, 0.35m mole) was dissolved in toluene and thermolysed by the general method for two weeks. The solvent was evaporated under reduced pressure, and the residue was dissolved in acidified ethanol (50ml). This solution was hydrogenated in the usual manner over 10% palladium charcoal powder (70mg). Examination of the product solution showed the presence of (di-p-tolylmethyl)-cyclopentane (21%) and 1-p-tolyl-5-methyl-1H-cyclopenta-[b]-indane (39%).

vi) Decomposition in Benzene (reflux temperature 78°)

Benzodiazepine (100mg, 0.35m mole) was dissolved in benzene and thermolysed for 30 days. The solvent was evaporated under reduced pressure and the residue was chromatographed on alumina (10" x ¼").

Fraction 1: petrol:hydrocarbon products, 23mg (26%)

Fraction 2: 5% benzene in petrol:unreacted diazepine 49mg (49%)

Fraction 3: ether; unidentified oil, 23mg

Fraction 1, (23mg) was dissolved in benzene (5ml) and ethanol (10ml) added. This solution was hydrogenated over 10% palladium charcoal powder (20mg) in the usual manner/...

manner. Examination of the product solution by glc and glc-ms showed the presence of only one product viz. (di-p-tolylmethyl)cyclopentane in estimated quantitative yield.

Thermolysis of 1,2,3,3a-Tetrahydro-7-fluoro-10-(p-fluorophenyl)benzo-[c]-cyclopenta-[f]-1,2-diazepine in Xylene Solution

a) The benzodiazepine (100mg, 0.34m mole) was dissolved in xylene (50ml) and thermolysed in the usual manner for 3 days. The solvent was evaporated under reduced pressure and the nmr spectrum of the crude product mixture obtained.

NMR Spectrum (CCl_4): characteristic peaks are 3.84τ, (m), and 3.88τ, (m), olefinic protons of 3-di-p-fluorophenyl-cyclopent-1-ene

5.9τ, (m), benzylic proton of 1,2,3,8-tetrahydro-5-fluoro-8-(p-fluoro)phenylcyclopenta-[b]-indene

6.46τ, (m), benzylic proton of 1,2,3,3a-tetrahydro-5-fluoro-8-(p-fluoro)phenylcyclopenta-[a]-indene

The solvent was again evaporated, and the residue dissolved in acidified ethanol (25ml). The solution was hydrogenated as usual over 10% palladium charcoal powder (70mg). Examination of the product by glc and glc-ms showed the presence/...

presence of two products, tentatively identified as (di-p-fluorophenylmethyl)cyclopentane (20%) and 1-p-fluorophenyl-5-fluoro-1H-cyclopenta-[b]-indane (36%) (by analogy with unsubstituted and dimethyl-substituted cases).

b) Benzodiazepine (100mg, 0.34m mole) was dissolved in xylene (100ml) and thermolysed as usual for 90h. The solvent was evaporated under reduced pressure and the residue dissolved in acidified ethanol (30ml). This was hydrogenated in the usual manner over 10% palladium charcoal powder (60mg). GLC and glc-ms then showed a product distribution of (di-p-fluorophenylmethyl)cyclopentane (18%) and 1-p-fluorophenyl-5-fluoro-1H-cyclopenta-[b]-indane (50%).

CIDNP Study of the Isomerisation of 1,2,3,3a-Tetrahydro-10-phenyl-benzo-[c]-cyclopenta-[f]-1,2-diazepine to 3-Phenyl-3-(cyclopent-1-enyl)-3H-indazole

1,2,3,3a-Tetrahydro-10-phenylbenzo-[c]-cyclopenta-[f]-1,2-diazepine (29.6mg, 0.114m mole) was weighed accurately into an nmr tube and dodecane (0.5195g) added. This mixture was heated to 120° in the probe of the nmr spectrometer to effect a homogeneous solution. The region 1-5 was continuously scanned while the probe was gradually heated to 180°. The resonances at 2.0τ and 4.4τ due to the low field aromatic and olefinic protons respectively/...

respectively of the indazole were seen to appear as the resonance at 2.4τ due to the low field aromatic proton of the diazepine disappeared. No CIDNP signal was observed.

Kinetics of Isomerisation of 1,2,3,3a-Tetrahydro-10-phenylbenzo-[c]-cyclopenta-[f]-1,2-Diazepine to 3-Phenyl-3-cyclopent-1-enyl-3H-indazole

i) Preliminary Experiments

HSLC separation of the two isomers was achieved using a 66mm glass column of internal diameter 2.1mm packed with CORASIL II of particle diameter 37-44μm. No fixed phase was used and the mobile phase was a 40% mixture of water-saturated n-hexane in 50% water-saturated methylene chloride. This constant polarity solvent was used throughout and the temperature was ambient. The internal standard was found by trial and error. Having obtained a separation between indazole, diethyl phthalate (the standard) and the diazepine, two preliminary reactions were carried out in nmr tubes side by side in a solvent bath at 165^{o}. One nmr tube contained diazepine (31.8mg, 0.12m mole) and dodecane (0.455g), the other, diazepine (30.6mg, 0.119m mole), diethyl phthalate (29.8mg, 0.135m mole) and dodecane (0.42g). Peak area ratios of I:D after identical times were identical for the two reactions showing that diethyl phthalate did not interfere with the reaction.

A/...

A series of synthetic mixtures was then made up as follows:

Mixture (1): Indazole: 50.7mg, 0.195m mole
Diazepine: 25mg, 0.0961m mole
Diethyl Phthalate: 87.4mg, 0.394m mole

Mixture (2): Indazole: 50.6mg, 0.195m mole
Diazepine: 24.95mg, 0.0959
Diethyl Phthalate: 122.2mg, 0.551m mole

Mixture (3): Indazole: 50.5mg, 0.194m mole
Diazepine: 24.9mg, 0.0957m mole
Diethyl Phthalate: 159.7mg, 0.906m mole

Mixture (4): Indazole: 50.4mg, 0.194m mole
Diazepine: 24.85mg, 0.0956m mole
Diethyl Phthalate: 243.2mg, 1.096m mole

These were diluted with the HSLC solvent (10ml) and high speed liquid chromatograms obtained, peak areas being measured using a Kent Chromalog II electronic integrator. This gave peak area ratios as follows:

	$I/_S$	$D/_S$
Mixture (1)	2.231	2.243
Mixture (2)	1.731	1.788
Mixture (3)	1.307	1.327
Mixture (4)	0.887	0.831

where/...

where I = Area of indazole peak

D = Area of diazepine peak

S = Area of diethyl phthalate peak

A plot of $\frac{\text{m Moles of compound}}{\text{m Moles of standard}}$ against $\frac{\text{Peak Area of compound}}{\text{Peak Area of standard}}$ then gave the straight line graphs shown in fig. (xvi) (see Discussion). This then served as the calibration graph for the kinetics experiments.

ii) Kinetics Experiments

Run (1): Reaction was carried out in a small thermostatted bath at 131.1 ± 0.3°C. The reaction vessel was a three-necked test-tube, the three necks carrying respectively a condensor and nitrogen inlet, a paddle stirrer and a septum cap. The benzodiazepine (150mg, 0.588m mole) and diethyl phthalate (423.7mg, 1.909m mole) were weighed accurately into the reaction vessel, and dry, n-hexadecane (15.0ml) added from a grade B pipette. The reaction vessel, with all its fitments was immersed rapidly in the oil-bath, to a level such that all of the solvent was under the surface of the oil-bath. The stop-clock was started on immersion of the reaction vessel, and 10µl samples of the reaction mixture were withdrawn at convenient times. Each sample was rapidly quenched in the HSLC solvent (0.25ml) and chromatograms obtained immediately/...

immediately. The concentrations of the diazepine and indazole in each sample were found and plotted against time. A full treatment of results is given in the Discussion of this work.

Run (2): This was carried out in a new thermostat bath with a better temperature control at 131.4 ± 0.05°C. The indazole (150mg, 0.588m mole) and diethyl phthalate (428.3mg, 1.929m mole) were weighed accurately into the reaction vessel and dry n-hexadecane (15.0ml) added. Reaction was carried out as described in run (1) and results are discussed in the Discussion section.

Photolysis of 3H-1,2-Benzodiazepines and their Tosyl-hydrazone Salt Precursors

a) Photolysis of 3H-1,2-Benzodiazepines

Direct Photolysis of 1,2,3,3a-Tetrahydro-10-phenyl-benzo-[c]-cyclopenta-[f]-1,2-diazepine

The diazepine (100mg, 0.385m mole) was dissolved in dry, freshly-distilled, deoxygenated 1,2-dimethoxyethane (100ml) and this solution was photolysed with the medium pressure lamp at room temperature under an atmosphere of dry oxygen-free nitrogen, through pyrex. After 1h, TLC on alumina (benzene) showed that all of the diazepine had reacted. The solvent was evaporated under reduced pressure and the residue was hydrogenated over 10% palladium charcoal powder (50mg) in acidified ethanol (25ml) at four atmospheres for 4 hours. The solvent was evaporated

after/...

after filtration, and the residue was vacuum-distilled to give a mixture of 1-phenyl-1H-cyclopenta-[b]-indane and 9-cyclopentylfluorene (70mg, 90%), bp 100-120°/0.1mm Hg. The ratio of the products was found to be 1:2.2 by glc (1% SE30, 170°).

Direct Photolysis of 1,2,3,3a-Tetrahydro-7-methyl-10-(p-tolyl)benzo-[c]-cyclopenta-[f]-1,2-diazepine

The benzodiazepine (50mg, 0.174m mole) was photolysed as in the previous experiment for 1h. Hydrogenation of the product mixture was effected in acidified ethanol (25ml), again as above. Investigation of the mixture by glc (1% SE30, 180°) identified the products as (35b) and (37b) in the ratio 1:2 although the absolute yields were not determined.

Benzophenone-Sensitised Photolysis of 1,2,3,3a-Tetrahydro-10-phenylbenzo-[c]-cyclopenta-[f]-1,2-diazepine

The benzodiazepine (100mg, 0.38m mole) and benzophenone (138mg, 0.76m mole) were dissolved in dry, deoxygenated dimethoxyethane (100ml) and photolysed with the medium pressure lamp at room temperature under an atmosphere of dry, oxygen-free nitrogen, and through a pyrex filter for 4h. The solvent was evaporated under reduced pressure and the oily residue (309mg) was dissolved in ethanol/...

ethanol (50ml). This solution was hydrogenated over 10% palladium charcoal powder (150mg) at four atmospheres for 4h. The product solution was analysed by glc (1% SE30, 170°) to show ten product peaks, two of which corresponded with the cyclopentaindane and fluorene products. Because of the complexity of the mixture, no further analysis was attempted.

b) Photolysis of 2-Diphenylmethylenecyclopentanone Toluene-p-sulphonylhydrazone Sodium Salt

GENERAL PROCEDURE. The sodium salt was made in the usual way by stirring a 5% molar excess of the tosylhydrazone in a freshly-made solution of sodium ethoxide in ethanol for 0.5h at room temperature. The ethanol was evaporated under reduced pressure and freshly-distilled, dry 1,2-dimethoxyethane was added to dissolve the salt. This solvent was then evaporated under reduced pressure to remove the last traces of ethanol, and the residual salt was dried for at least 10h under high vacuum over fresh P_2O_5. The salt was then dissolved in dry, freshly-distilled 1,2-dimethoxyethane (100ml) and the solution photolysed with the medium pressure lamp through pyrex or quartz and in the presence or absence of sensitiser as required. The time of reaction was usually between 1h and 3h. The photolyses were carried out at room temperature and under an atmosphere of dry oxygen-free nitrogen/...

nitrogen. The precipitated sodium sulphinate was filtered off. After glc analysis of the solution, the solvent was evaporated under reduced pressure, and the residue was hydrogenated in the usual manner. The hydrogenation products were then identified by glc analysis and glc-mass spectral data, or as stated in individual examples.

i) Benzophenone-Sensitised Photolysis through Pyrex

The sodium salt was prepared and dried in the usual manner from sodium (0.019g, 0.00083 mole) and 2-diphenylmethylenecyclopentanone tosylhydrazone (0.342g, 0.00083 mole). The salt was dissolved in DME and benzophenone (0.300g, 0.0016 mole) added. This solution was photolysed through pyrex for two hours, (and hydrogenated in the usual manner). The solvent was evaporated after filtration and the residue dry-column chromatographed on alumina using n-hexane as eluting solvent. The yield of eluted hydrocarbons was (38.5mg, 20%) and these were identified by glc as diphenylmethylcyclopentane and 1-phenyl-1H-cyclopenta-[b]-indane in the ratio 1:5.

ii) Benzophenone-Sensitised Photolysis through quartz

The lithium salt was prepared rather than the sodium salt, from 2-diphenylmethylenecyclopentanone tosylhydrazone (632mg, 1.5m mole) and butyl lithium (0.86ml, of 15% solution/...

solution in hexane) in DME (100ml). Dry benzophenone (366mg, 2m mole) was added and the resulting solution photolysed for 1h and then hydrogenated in the usual manner. The hydrogenation mixture was filtered, the solvent evaporated and the residue dry-column chromatographed on alumina using n-pentane as eluting solvent. The hydrocarbon band was vacuum dried to leave a mixture of (diphenylmethyl)cyclopentane and 1-phenyl-1H-cyclopenta-[b]-indane (116mg, 33%) in the ratio 1:5.

iii) Direct Photolysis through Pyrex

The sodium salt, prepared from sodium (0.10g, 0.0043 mole) and 2-diphenylmethylenecyclopentanone tosylhydrazone (1.81g, 0.0043 mole), was photolysed through pyrex as described in the general method. Reaction was complete after 2h and the solution was filtered to remove the sodium sulphinate (0.623g, 81%). The filtrate was left open to the air for 3 days (see Discussion), and the solvent was evaporated under reduced pressure. The residue was chromatographed on alumina (1% ether in cyclohexane) to give a mixture of (diphenylmethyl)cyclopentane and 1-phenyl-1H-cyclopenta-[b]-indane (100mg, 25%) in the ratio 1:6, followed by a white crystalline solid which was recrystallised from ethanol to give 1-phenyl-6,7-benzobicyclo-[3,2,1]-octan-2-one (638mg, 69%) as white needles, mp 159-161.

IR Spectrum (Nujol): 1750cm^{-1}, C = O

NMR Spectrum: See Appendix I.II

Mass Spectrum: See Appendix I.12

Mass Measurement: Found: M^+ = 248.120149
$C_{18}H_{16}O$ requires M^+ = 248.120109

Preparation of Reference Compounds

3-Diphenylmethylenecyclopent-1-ene

2-Diphenylmethylenecyclopentanone toluene-p-sulphonylhydrazone (416mg, 1m mole) was dissolved in dry, freshly-distilled DME (25ml) and butyllithium solution (2ml) added. The solution was stirred at room temperature under an atmosphere of dry, oxygen-free nitrogen for two days then poured into water (100ml) and extracted with ether (3 x 25ml). After drying, the ether was evaporated under reduced pressure and the residue distilled to afford a low-melting off-white waxy solid bp 110°/ 0.001mm Hg, mp = 48-50° which proved to be 3-diphenylmethylenecyclopent-1-ene (174mg, 75%).

Found: C 92.8% HH 7.0% $C_{18}H_{16}$ requires C 93.1% H 6.9%

NMR Spectrum (CCl_4): 2.86τ, (m), 10H; 3.64τ, (m), 1H; 3.88τ, (m), 1H; 7.16-7.8τ, (m), 4H

Mass Spectrum: see Appendix I.6.

Diphenylmethylcyclopentane

3-Diphenylmethylenecyclopent-1-ene (90mg, 0.39m mole) was dissolved in ethanol (20ml) containing conc. hydrochloric acid (1 drop) and hydrogenated over 10% palladium charcoal powder (140mg) for four hours at four atmospheres pressure. GLC (1% SE30, 190°) and GLC-MS showed a single product of molecular weight 236. The reaction mixture was filtered through celite, and the filtrate was evaporated under reduced pressure. The residue was vacuum-distilled to afford diphenylmethylcyclopentane (87mg, 95%) as a colourless oil bp = 110°/0.001mm Hg.

Found: C 92.4% H 7.5% $C_{18}H_{20}$ requires C 92.3% H 7.7%

NMR Spectrum (CCl_4): 3.0τ, (m), 10H; 6.58τ, (d J=11cps), 1H; 7.4τ, (m), 1H; 8.2τ-9.1τ, (m), 8H

3-(Di-p-tolyl)methylenecyclopent-1-ene

2-Di-p-tolylmethylenecyclopentanone toluene-p-sulphonylhydrazone (444mg, 1m mole) in ether (20ml) was dripped onto butyllithium solution (3ml), slowly at room temperature and under an atmosphere of dry oxygen-free nitrogen. The solution was stirred for 36h then poured into water (20ml) and the layers separated. The aqueous solution was extracted with ether (1 x 20ml), the ether extracts combined/...

combined and dried over anhydrous magnesium sulphate. The solvent was evaporated under reduced pressure and the residue was vacuum-distilled to afford 3-(di-p-tolyl-methylene)cyclopent-1-ene (204mg, 75%) as a colourless oil (bp = 110°/0.001mm Hg) which solidified on standing to a white waxy solid (mp = 62-64°).

Found: C 92.2% H 7.7% $C_{20}H_{20}$ requires C 92.3% H 7.7%

NMR Spectrum (CCl_4): 3.02τ, (m), 8H; 3.66τ, (m), 1H; 3.96τ, (m), 1H; 7.4τ, (m), 4H; 7.7τ, (s), 6H

(Di-p-tolylmethyl)cyclopentane

(3-Di-p-tolylmethylene)cyclopent-1-ene (103mg, 0.39m mole) was dissolved in ethanol (20ml) containing conc. hydrochloric acid (0.1ml) and hydrogenated at four atmospheres over 10% palladium charcoal powder (140mg) for 4h. Examination by glc and glc-ms (1% SE30, 190°) showed a single peak product of molecular weight 264. The reaction mixture was filtered through celite and the solvent evaporated under reduced pressure. The residue was vacuum-distilled to afford (di-p-tolylmethyl)cyclopentane (100mg, 97%) as a colourless oil bp 110-116°/0.001mm Hg.

Found: C 91.8% H 8.5% $C_{20}H_{24}$ requires C 91.6% H 8.4%

NMR Spectrum (CCl_4): 3.0τ, (m), 8H; 6.58τ(d, J=11cps), 1H; 7.4τ, (m), 1H; 7.74τ, (s), 6H; 8.2τ-9.1τ, (m), 8H

1,2,3,8-Tetrahydro-8-phenylcyclopenta-[b]-indene

This compound was prepared by a five-stage synthesis as follows.

(i) Adipyl Chloride[93]: Adipic acid (112.7g, 0.77 mole) was added to a flask containing thionyl chloride (270ml, 4 moles) in benzene (300ml). This mixture was heated under reflux overnight. The benzene was evaporated under reduced pressure and the crude product vacuum-distilled to afford adipyl chloride (134g, 97%) colourless oil bp 100°/ 1.5mm Hg (lit[93]., 130-132°/18mm Hg)

(ii) 1,4-Dibenzoylbutane[93]: Aluminium chloride (237g, 1.78 moles) in benzene (1100ml) was cooled in an ice bath and then adipyl chloride (142g, 0.77 mole) added with rapid stirring over a period of 1h. When the addition was complete, the ice bath was removed and the stirring was continued at room temperature for 2h. The solution was then poured onto a mixture of conc. hydrochloric acid (200ml) and crushed ice (1000g). Benzene (1500ml) was added, and the mixture heated gently to dissolve the product. The layers were separated and the benzene extract washed with dilute sodium carbonate solution (1 x 500ml), then water (1 x 100ml). After drying, ($MgSO_4$), the solvent was evaporated under reduced pressure till the volume was about 300ml whereupon crystallisation of the product occurred on standing overnight/...

overnight. The yield of 1,4dibenzoylbutane (mp 105-107°; lit[93],104-107°) was (154g, 73%).

(iii) 1-Benzoyl-2-phenylcyclopent-1-ene[94]: 1,4-Dibenzoylbutane (52g, 0.2 mole) and potassium hydroxide pellets (43g) were heated under reflux in ethanol (1000ml) for 52h. Most of the ethanol was evaporated under reduced pressure, and the remaining solution was poured into water (100ml) and extracted with ether (3 x 50ml). The extracts were combined, dried, filtered and the solvent evaporated under reduced pressure. The residue was vacuum-distilled to afford a mixture of 1-benzoyl-2-phenylcyclopent-1-ene an-3-benzoyl-2-phenylcyclopent-1-ene. Storage in the deep freeze at -26° under ether caused preferential precipitation of 1-benzoyl-2-phenylcyclopent-1-ene as a low-melting waxy solid. This was recrystallised from ethanol to give a purer product (8.0g, 16%) mp = 65-67° (lit.,[94] 68°) as off-white prisms.

(iv) 1-Benzoyl-2-phenylcyclopent-1-ene Toluene-p-sulphonylhydrazone[95]: 1-Benzoyl-2-phenylcyclopent-1-ene (3.92g, 0.016 mole) was dissolved in ethanol (25ml) and stirred at room temperature. Toluene-p-sulphonylhydrazide (3.21g, 0.017 mole) was also dissolved in ethanol (25ml). The two solutions were mixed and heated to 60° after which the mixture was stirred at room temperature for five days. After/...

After this time, there was no sign of a precipitate so conc. hydrochloric acid (5 drops) was added. Stirring was continued for 15 days and the precipitate which formed was filtered off from time to time until the mother liquor became a deep reddish-brown colour. Most of the tosylhydrazone had formed by then. No attempt was made to purify this tosylhydrazone other than vacuum drying because of its thermal instability.

(v) 1,2,3,8-Tetrahydro-8-phenylcyclopenta-[b]-indene[95]: The sodium salt of 1-benzoyl-2-phenylcyclopent-1-ene tosylhydrazone was prepared in the usual way by stirring the tosylhydrazone (0.613g, 1.47m mole) in a solution of sodium (0.0339g, 1.47m mole) in ethanol (50ml) for 30 minutes. After evaporation of the solvent and drying in the usual manner, freshly distilled cyclohexane (75ml) was added, and the resulting solution heated under reflux under an atmosphere of dry oxygen-free nitrogen for 24h in the dark. The precipitated sodium sulphinate was filtered off and discarded. The solution was evaporated to dryness under reduced pressure, and the residue was vacuum-distilled to afford 1,2,3,8-tetrahydro 8-phenylcyclopenta-[b]-indene (300mg, 88%) as a colourless oil bp = 100°/0.1mm Hg (lit.,[25] 100°/0.1mm Hg).

NMR Spectrum (CCl_4): See Appendix I.5

1-Phenyl-1H-cyclopenta-[b]-indane[95]: 3-Phenyl-3H-cyclopenta-[a]-indene (50mg, 0.22m mole) was dissolved in ethanol (40ml) containing conc. hydrochloric acid (1 drop) and 10% palladium charcoal powder (40mg) added. The mixture was hydrogenated at four atmospheres for 4h. Examination of the solution by glc and glc-ms (1% SE30, 170°) showed a single peak product of molecular weight 234. The palladium charcoal was filtered off through a pad of celite and the filtrate evaporated to dryness to give 1-phenyl-cyclopenta-[b]-indane in an analytically pure state.

Found: C 92.1% H 7.8% $C_{18}H_{18}$ requires C 92.3% H 7.7%

NMR Spectrum: See Appendix I.3

9-Cyclopentylidene Fluorene

Butyllithium solution (25ml) was added to fluorene (6g, 0.036 mole) in dry, deoxygenated cyclohexane (100ml) under an atmosphere of dry oxygen-free nitrogen, and the mixture was heated under reflux for 0.75h. Cyclopentanone (3.06g, 0.036 mole) in cyclohexane (20ml) was added dropwise and the solution heated under reflux for two days. After cooling, conc. hydrochloric acid (5ml) in ethanol (100ml) was added and the solution heated under reflux for a further 12h. The solution was extracted with chloroform (2 x 50ml) and the extract dried/...

dried over anhydrous magnesium sulphate. The solution was filtered and the solvent evaporated under reduced pressure whereupon the residue was chromatographed on alumina.

Fraction 1: petroleum; unreacted fluorene (3.4g, 53%)

Fraction 2: 1-10% ether in petroleum; white amorphous solid which was recrystallised from ethanol to afford 9-cyclopentylidene fluorene (1.41g, 12% based on total fluorene) as colourless needles mp = 146-149°.

Found: C 92.8% H 7.0% $C_{18}H_{16}$ requires C 93.1% H 6.9%

NMR Spectrum: See Appendix I.5

Mass Spectrum: See Appendix I.6

9-Cyclopentylfluorene

9-Cyclopentylidenefluorene (80mg, 0.34m mole) was hydrogenated at four atmospheres over 10% palladium charcoal powder (100mg) in acidified ethanol (30ml) for four hours. After filtration through celite, the solvent was evaporated under reduced pressure and the residue chromatographed on a short dry column alumina, to afford a quantitative yield of 9-cyclopentylfluorene, analytically pure, as colourless needles mp = 60-62° (lit.,[91] 60-62.4°).

Found: C 92.3% H 7.7% $C_{18}H_{18}$ requires C 92.2% H 7.8%

NMR Spectrum: See Appendix I.3

Mass Spectrum: See Appendix I.6

Miscellaneous Experiments

Gas phase pyrolysis of 3-Diphenylmethylenecyclopent-1-ene

3-Diphenylmethylenecyclopent-1-ene (28mg, 0.12m mole) was pyrolised under identical conditions to those used for the benzodiazepines at 400°. The product oil (26mg) was collected and its nmr spectrum obtained.

NMR Spectrum (CCl_4): 2.86τ, (m) aromatic (24H)
3.64τ, (m) olefinic (1H)
3.88τ, (m) olefinic (1H)
7.16τ-7.8τ, (m) aliphatic (12H)

This indicated that 3-Diphenylmethylenecyclopent-1-ene was not isomerised on heating to 400° although some polymerisation had occurred.

Gas phase pyrolysis of 3-Phenyl-3H-cyclopenta-[a]-indene

3-Phenyl-3H-cyclopenta-[a]-indene (100mg, 0.43m mole) was pyrolysed under the same conditions as were the benzodiazepines at 400° in the gas phase. The product (quant.) was collected and shown to be unchanged starting material by/...

by its nmr spectrum.

NMR Spectrum (CCl_4): 2.9τ, (m), 9H; 5.76τ, (m), 1H; 7.2τ-7.8τ, (m), 6H

Gas phase pyrolysis of 9-Cyclopentylidenefluorene

9-Cyclopentylidenefluorene (100mg, 0.43m mole) was pyrolysed in the gas phase under identical conditions to those employed in benzodiazepine pyrolysis at 400°. The product (quant.) was collected and its nmr spectrum obtained.

NMR Spectrum (CCl_4): 2.4τ, (m), 4H; 2.82τ, (m), 4H; 7.0τ, (m), 4H; 8.13τ, (m), 4H

This showed the product to be unchanged 9-cyclopentylid nefluorene.

Gas phase pyrolysis of 9-Cyclopentylidenefluorene over alumina at 400°

Alumina (15g) was heated to 450° under vacuum for four hours in the furnace of the pyrolysis unit. The temperature was then allowed to equilibrate to 400° and 9-cyclopentylidenefluorene (200mg, 0.86m mole) was pyrolysed in the usual manner for 16h. The product trap was washed out with chloroform and the solvent removed under reduced pressure to afford 9-cyclopentylidenefluorene (200mg, quantitative) as a white micro-crystalline powder.

NMR Spectrum (CCl_4): 2.4τ, (m), 4H; 2.82τ, (m), 4H; 7.0τ, (m), 4H; 8.13τ, (m), 4H

Attempted acid-catalysed isomerisation of 9-cyclopentylidenefluorene

This reaction was done on a glc scale only. 9-Cyclopentylidenefluorene (5mg, 0.022m mole) in ethanol (2ml) containing conc. hydrochloric acid (1 drop) was heated under reflux for 12h. GLC (1% SE30, 190°) analysis showed a single peak peoduct of identical retention time as 9-cyclopentylidenefluorene.

Attempted base-catalysed isomerisation of 9-cyclopentylindinefluorene

A microspatula tipful of sodium was dissolved in "super-dry" ethanol (2ml) and 9-cyclopentylidenefluorene (5mg, 0.022m mole) was added. The resulting solution was heated under reflux for 12h then analysed by glc (1% SE30, 190°). This showed a single peak of retention time identical to that of 9-cyclopentylidenefluorene.

Reaction of the product mixture from the gas phase pyrolysis of 1,2,3,3a-Tetrahydro-10-phenylbenzo-[c]-cyclopenta-[f]-1,2-diazepine with acid and with base

The pyrolysate from the reaction of 1,2,3,3a-tetrahydro-10-phenylbenzo-[c]-cyclopenta-[f]-diazepine (220mg, 0.85m mole) at 400° in the gas phase was made up to 10ml with ethanol and split into two 5ml fractions, one of which was heated under reflux along with conc. hydrochloric acid/...

acid (0.2ml) for 12h. Analysis by glc (1% SE30, 180°) showed that no reaction had occurred. The acid was neutralised, and dilute sodium ethoxide solution (2ml) was added. This solution was, in turn, heated under reflux for 12h. Examination by glc (1% SE30, 180°) now showed that the peak due to 9-cyclopent-1-enylfluorene had disappeared completely, and a new peak had appeared at the same retention time as 9-cyclopentylidinefluorene. The solution was made acidic once more with conc. hydrochloric acid and hydrogenated over 10% palladium charcoal powder (100mg) for 4h at four atmospheres. The second 5ml fraction had meanwhile been hydrogenated under identical conditions. Analysis of both solutions by glc (1% SE30, 180°) gave identical chromatograms containing two peaks only. These were due to 1-phenyl-1H-cyclopenta-[b]-indane and 9-cyclopentylfluorene respectively.

APPENDIX I.1

Synthesis of 1,2,3,3a-Tetrahydro-7-fluoro-10-(p-fluoro)-phenylbenzo-[c]-cyclopenta-[f]-1,2-Diazepine

This compound was prepared by Mr. G.M. Baird[96] as part of his honours project. The preparation was exactly analogous to that of the unsubstituted compound:

2-(Di-p-fluorophenyl)methylenecyclopentanone

The Grignard reagent was prepared from p-fluorobromobenzene (29.96g, 0.154 mole) and magnesium (4g, 0.167 mole) in dry ether 150ml. After addition of all the bromo-compound , the mixture was heated under reflux for 30 minutes. 2-Ethylenedioxyethoxycarbonylcyclopentane (14g, 0.07 mole) in ether (150ml) was added dropwise with vigorous (mechanical) stirring and the mixture was heated under reflux overnight. After cooling, ammonium chloride (60g) in water 200ml was added, with stirring. The layers were separated, and the aqueous extracted with ether (2 x 150ml). The ether extracts were combined, washed with water (1 x 150ml) and dried over anhydrous magnesium sulphate. After filtration, the ether was evaporated under reduced pressure to afford a reddish-yellow oil. To this oil was added ethanol (100ml), water (100ml) and conc. hydrochloric acid (3ml) and the mixture was heated under reflux with vigorous stirring/...

stirring for 4h then allowed to stand at room temperature overnight. The precipitated solid was filtered off and recrystallised from ethanol to give 2-di(-p-fluorophenyl)-methylenecyclopentanone (4.74g, 23.8%) as yellow needles mp 147-148°.

Found: C 76.1% H 4.9% $C_{18}H_{14}OF_2$ requires C 76.0% H 5.0%

IR (Nujol): 1710cm^{-1}, C = O

NMR ($CDCl_3$): 2.8-3.15τ, (m), 8H; 7.2τ, (t), 2H;
7.5-7.75τ, (m), 2H; 7.9-8.25τ, (m), 2H

Mass Spectrum: $(M+1)^+$=285(18%), M^+=284(100%),
$(M-1)^+$=283(96%) 256^+(90%), 255(7.5%),
242(14%), 241(10%), 228(54%), 227(50%)

2-(Di-p-fluorophenyl)methylenecyclopentanone Toluene-p-sulphonylhydrazone

2-(Di-p-fluorophenyl)methylenecyclopentanone (4.21g, 0.015 mole) in ethanol (60ml) was heated to 50° as was toluene-p-sulphonylhydrazide (2.79g, 0.015 mole) in ethanol (30ml) containing conc. hydrochloric acid (0.5ml). The two solutions were mixed and stirred for several minutes and the mixture was then allowed to stand overnight. The precipitate (5.48g, 81.7%) mp 204-206° (decomp.), was filtered off and dried under high vacuum. Owing to its instability, it was not attempted to recrystallise this/...

this compound.

Found: C 66.7% H 4.8% N 6.5% $C_{25}H_{22}N_2F_2SO_2$ requires
C 66.4% H 4.8% N 6.2%

IR (Nujol): 3200cm^{-1}, N-H; 1625cm^{-1}(w), C=N
1340cm^{-1}, 1160cm^{-1}, $S(=O)_2$

NMR ($CDCl_3$): 2.5 -2.8τ, (m), 4H; 2.8τ-3.2τ, (m), 8H; 2.8-3.2τ, (bs), 1H (N-H); 7.3-7.7τ, (m), 4H; 7.5τ, (s), 3H; 8.0-8.3τ, (m), 2H

Sodium salt of 2-(Di-p-fluorophenyl)methylenecyclopentanone Toluene-p-sulphonylhydrazone and its cyclisation to 1,2,3,3a-etrahydro-7-fluoro-10-(p-fluorophenyl)benzo-[c]-cyclopenta-[f]-1,2-diazepine

Sodium (0.097g, 0.00424 mole) was dissolved in "superdry" ethanol (100ml) and 2-di-p-(fluorophenyl)methylenecyclopentanone toluene-p-sulphonylhydrazone (2.097g, 0.00464 mole) added. The ethanol was evaporated under reduced pressure and the solid salt was dissolved in dry, freshly-distilled DME (100ml) which was immediately evaporated under reduced pressure again to give the solid salt which was free from ethanol. The salt was vacuum dried for 16h. Dry, freshly-distilled cyclohexane (150ml) was added, and the mixture was heated under reflux in darkness under an atmosphere of dry, oxygen-free nitrogen for 22h. The unwanted precipitate of sodium p-toluenesulphinate (0.89g) was/...

was filtered off and discarded. The cyclohexane solution was evaporated under reduced pressure and the yellow solid obtained was recrystallised from ethanol to afford 1,2,3,3a-tetrahydro-7-fluoro-10-(p-fluorophenyl)benzo-[c]-cyclopenta-[f]-1,2-diazepine (0.52g, 41.4%) as yellow needles mp 129-132°.

Found: C 72.9% H 5.1% N 9.4% $C_{18}H_{14}N_2F_2$ requires C 73% H 4.8% N 9.4%

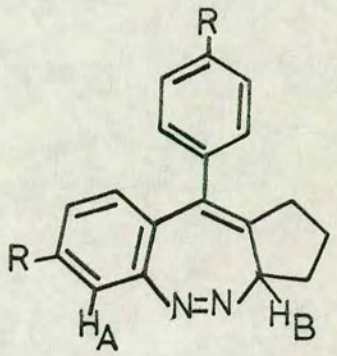
IR (Nujol): 1600cm^{-1}, N=N; 1560cm^{-1}, C=C

NMR ($CDCl_3$): 2.5τ, (m), 1H; 2.7-3.2τ, (m), 6H; 6.7-7.0τ, (m), 1H; 7.2-7.9τ, (m), 6H

Mass Spectrum: M^+=296(1%), 268(47%), 241(18%), 240(100%), 239(53%), 238(31%), 227(38%), 201(13%)

APPENDIX I.2

NMR Spectra of Benzodiazepines



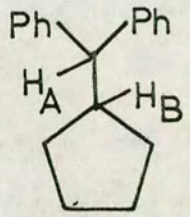
(5)

Compound	R	NMR Spectrum in CCl_4		Integration	Assignment
		Resonance	Line Pattern		
(5a)	H	2.24τ	m	1H	H_A
		2.8τ	m	8H	Aromatics
		6.84τ	m	1H	H_B
		7.1τ-8.1τ	m	6H	Aliphatics
(5b)	CH_3	2.44τ	m	1H	H_A
		2.95τ	m	6H	Aromatics
		6.88τ	m	1H	H_B
		7.2τ-8.1τ	m	12H	Aliphatics
(5c)	F	2.5τ *	m	1H	H_A
		2.95τ	m	6H	Aromatics
		6.85τ	m	1H	H_B
		7.2-7.9τ	m	6H	Aliphatics

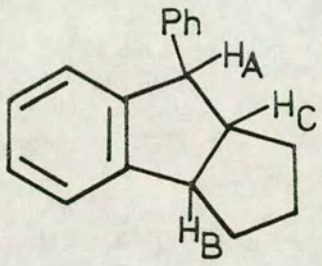
* Spectrum determined in $CDCl_3$ solution

APPENDIX I.3

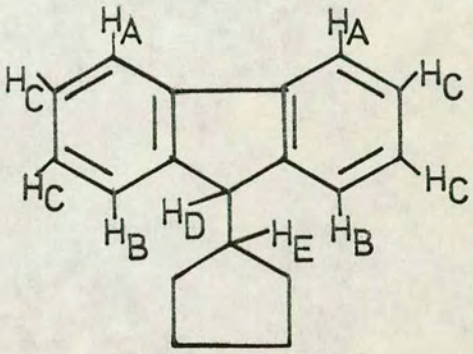
NMR Spectra of the Pyrolysis-Hydrogen Products obtained from (5a)



(38)



(8)



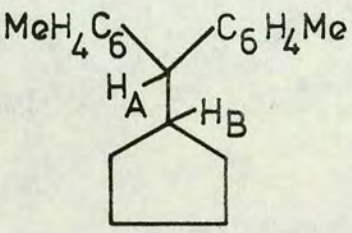
(9)

Compound	NMR Spectrum in CCl_4			
	Resonance	Line Pattern	Integration	Assignment
(38)	3.0τ	m	10H	Aromatics
	6.58τ	d, J=11cps	1H	H_A
	7.4τ	m	1H	H_B
	8.2-9.1τ	m	8H	Aliphatics
(8)	2.9τ	m	9H	Aromatics
	5.42τ	d, J=8cps	1H	H_A
	6.38τ	t of d, J=8cps J'=4cps	1H	H_B
	7.01τ	q*, J=8cps	1H	H_C
	7.6-9τ	m	6H	Aliphatics
(9)	2.37τ	m	2H	H_A
	2.58τ	m	2H	H_B
	2.80τ	m	4H	H_C
	6.08τ	d, J=5cps	1H	H_D
	7.66τ	m	1H	H_E
	8.1-9τ	m	8H	Aliphatics

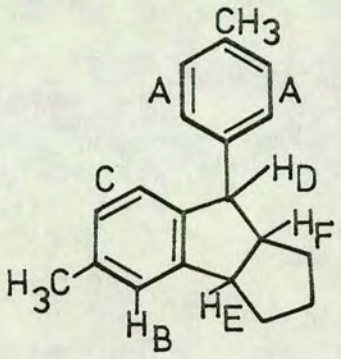
* quin.

APPENDIX I.4

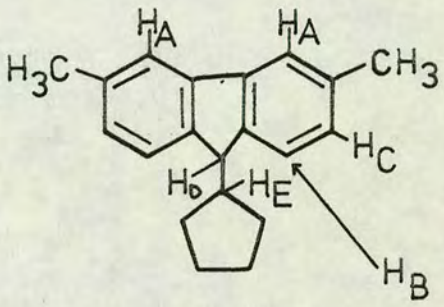
NMR Spectra of the Pyrolysis-Hydrogenation Products obtained from (5b)



(38b)



(35b)

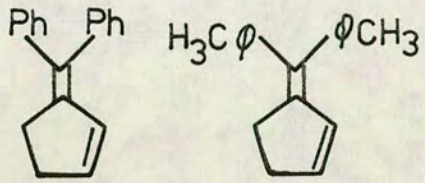


(37b)

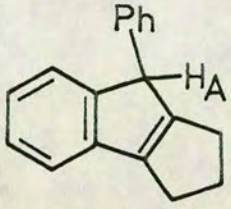
Compound	NMR Spectrum in CCl_4 Resonance	Line Pattern	Integration	Assignment
(38b)	3.0τ	m	8H	Aromatics
	6.58τ	d, J=11cps	1H	H_A
	7.4τ	m	1H	H_B
	7.74τ	s	6H	Methyls
	8.2-9.1τ	m	8H	Aliphatics
(35b)	3.02τ	s	4H	H_A
	3.09τ	s	1H	H_B
	3.17τ	s	2H	H_C
	5.50τ	d, J=8cps	1H	H_D
	6.44τ	t of d J=8cps, J'=4cps	1H	H_E
	7.04τ	quin.	1H	H_F
	7.70τ	s	6H	Methyls
	7.72τ-9.06τ	m	6H	Aliphatics
(37b)	2.59τ	bs	2H	H_A
	2.69τ	d, J=9cps	2H	H_B
	3.05τ	bd, J=9cps	2H	H_C
	6.16τ	d, J=8cps	1H	H_D
	7.61τ	s	6H	Methyls
	7.61τ	m	1H	H_E
	8.12-9.08τ	m	8H	Aliphatics

APPENDIX I.5

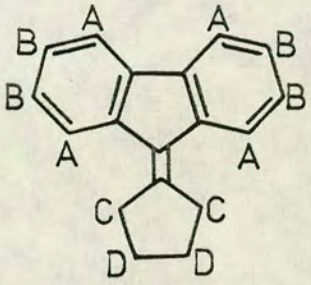
NMR Spectra of Authentic Alkenes



(41) (41b)



(12)

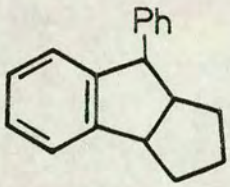


(13)

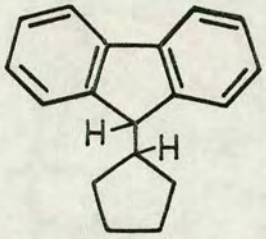
Compound	NMR Spectrum in CCl_4			
	Resonance	Line Pattern	Integration	Assignment
(41)	2.86τ	m	10H	Aromatics
	3.64τ	m	1H	H_A
	3.88τ	m	1H	H_B
	7.16τ-7.8τ	m	4H	Aliphatics
(41b)	3.02τ	m	8H	Aromatics
	3.66τ	m	1H	H_A
	3.96τ	m	1H	H_B
	7.2τ-7.9τ	m	4H	Aliphatics
	7.7τ	s	6H	Methyls
(12)	2.9τ	m	9H	Aromatics
	5.76τ	finely split m	1H	H_A
	7.2-7.8τ	m	6H	Aliphatics
(13)	2.4τ	m	4H	H_A
	2.8τ	m	4H	H_B
	7.0τ	m	4H	H_C
	8.1τ	m	4H	H_D

APPENDIX I.6

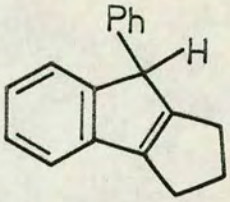
Mass Spectra of Products Related to (5a)



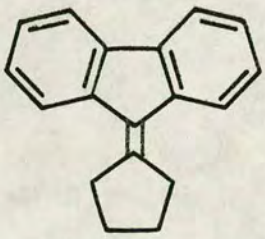
(8)



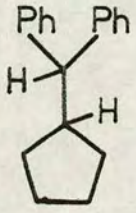
(9)



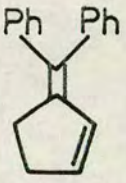
(12)



(13)



(38)

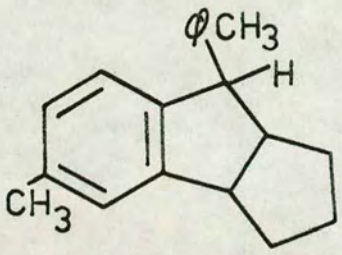


(41)

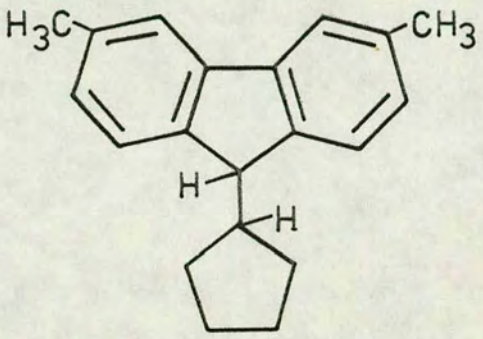
Compound	m/e (% Relative Abundance)
(8)	77(10), 91(27), 115(15), 128(17), 129(31), 191(32), 192(19), 204(36), 234(100)
(9)	165(82), 166(100), 234(46)
(12)	91(8), 202^{2+}(24), 191(21), 204(100), 215(16), 232(91)
(13)	91(1), 202^{2+}(3), 165(50), 166(27), 179(14), 191(100), 202(17), 203(18), 204(17), 215(13), 232(91)
(38)	77(4), 91(22), 119(9), 153(23), 165(40), 166(16), 167(100), 168(78), 236(43)
(41)	77(25), 91(47), 202^{2+}(28), 115(28), 129(25), 141(30), 152(30), 165(33), 166(40), 191(100), 202(36), 204(33), 232(33)

APPENDIX I.7

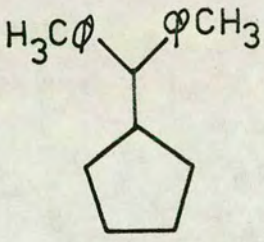
Mass Spectra of Hydrocarbon Products Related to (5b)



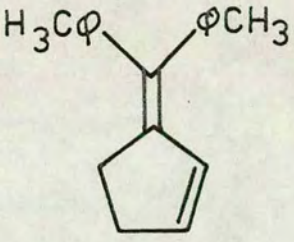
(35b)



(37b)



(38b)

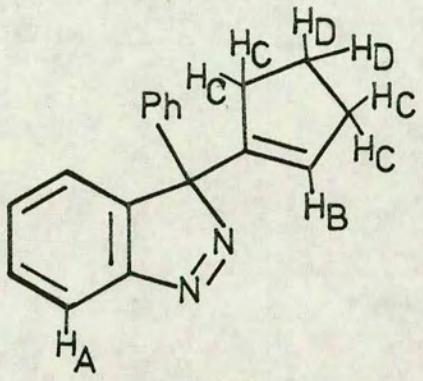


(41b)

Compound	m/e (% Relative Abundance)
(35b)	77(8), 91(13), 202^{2+}(14), 105(26), 129(45), 143(34), 155(15), 198(17), 247(100), 262(55)
(37b)	179(18), 180(14), 193(100), 194(59), 262(46)
(38b)	91(14), 165(50), 178(23), 179(27), 180(32), 181(20), 195(100), 196(93), 264(40)
(41b)	91(16), 165(12), 215(21), 219(18), 227(17), 230(17), 245(30), 260(100)

APPENDIX I.8

NMR Spectra of 3-Phenyl-3-(cyclopent-1-enyl)-3H-Indazole

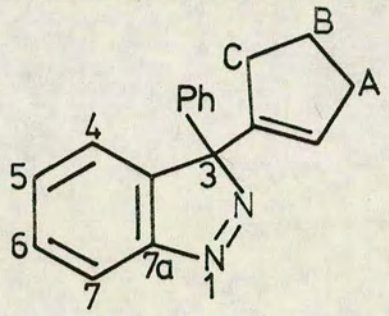


(55)

Resonance	Line Pattern	Integration	Assignment
2.0τ	m	1H	H_A
2.7τ	m	8H	Aromatics
4.4τ	finely split m	1H	H_B
7.68τ	t	4H	H_C
8.14τ	q	2H	H_D

APPENDIX I.9

^{13}C NMR Spectra of Benzodiazepines and Indazole

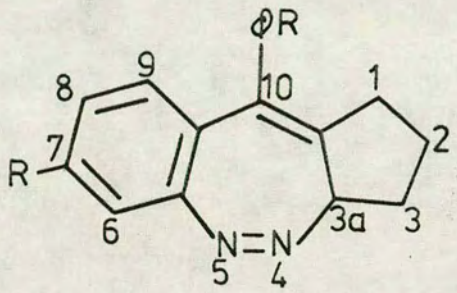


(55)

Resonance (ppm from TMS)	Assignment
23.2	C_B
32.2	C_A or C_C
32.6	C_A or C_C
99.8	C_3
121.9	Aromatic carbons + olefinic carbons
123.5	
126.7	
127.0	
127.9	
128.1	
128.4	
128.7	
129.4	
129.6	
135.3	quaternary carbon
139.9	" "
142.4	" "
156.1	C_{7a}

APPENDIX I.9 (continued)

^{13}C NMR Spectra of Benzodiazepines and Indazole



(5)

a) R = H

b) R = CH_3

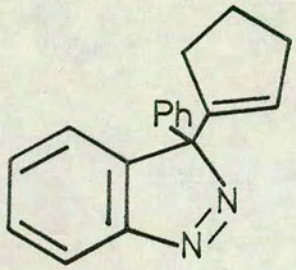
Compound	Resonance (ppm from TMS)	Assignment
(5a)	26.8	C_2
	32.4	C_3 or C_1
	32.6	C_3 or C_1
	74.6	C_{3a}
	125.5	Aromatic carbons + 1 quaternary carbon
	126.8	
	127.3	
	127.4	
	127.6	
	128.1	
	128.6	
	129.0	
	129.9	
	130.2	

APPENDIX I.9 (continued)

Compound	Resonance (ppm from TMS)	Assignment
(5a)	132.6	quaternary carbon
	139.3	quaternary carbon
	143.3	quaternary carbon
	152.0	C_{6a}
(5b)	20.5	Methyl
	21.1	Methyl
	26.8	C_2
	32.2	C_3 or C_1
	32.6	C_3 or C_1
	74.5	C_{3a}
	127.1 127.9 128.1 128.7 128.9 129.4 129.7 130.1	Aromatic carbons + 1 quaternary carbon
	132.4	quaternary carbon
	135.3	quaternary carbon
	136.4	quaternary carbon
	136.8	quaternary carbon
	141.7	quaternary carbon
	151.8	

APPENDIX I.10

Mass Spectrum of 3-Phenyl-3-(cyclopent-1-enyl)-3H-Indazole

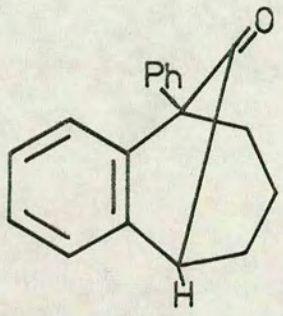


(55)

m/e	% Relative Abundance
260	not observed
232	100
204	41.8
191	41.8
165	22.6
202^{2+}	14.8
77	5.8
67	8.7

APPENDIX I.11

NMR Spectrum of 1-Phenyl-6,7-benzobicyclo-[3,2,1]-octan-8-one

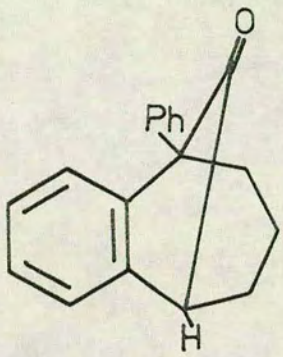


(63)

Solvent	Resonance	Line Pattern	Integration
	2.8	(m)	8
	3.2	(m)	1H
CCl_4	6.5	apparent triplet	1H
	7.7	(m)	2H
	8.0	(m)	2H
	8.4	(m)	2H
	2.8	(s)	5H
	3.0	(m)	3H
C_6D_6	3.32	(m)	1H
	6.64	two overlapping doublets	1H
	7.86 -8.8	(m)	6H

APPENDIX I.12

Mass Spectrum of 1-Phenyl-6,7-benzobicyclo-[3,2,1]-octan-8-one



(63)

m/e	% Relative Abundance
248	45
220	100
205	65
220	41
129	45

D I S C U S S I O N

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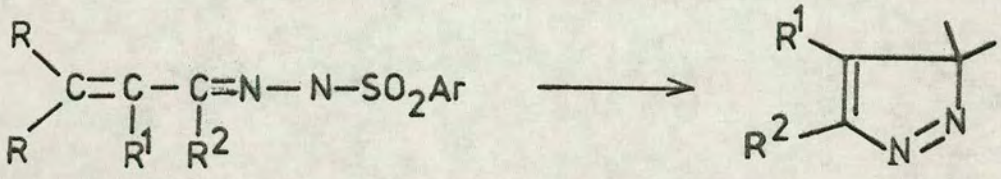
D I S C U S S I O N

Preamble: The thermal decompositions of the sodium salts of toluene-p-sulphonylhydrazones of α,β-unsaturated carbonyl compounds are well known to give cyclic products such as 3H-pyrazoles, 1H-pyrazoles and cyclopropenes. For example Closs and Böll[97] showed that the toluene-p-sulphonylhydrazone sodium salts of some open chain and cyclic ketones were readily cyclised to 3H-pyrazoles on heating to 130° under high vacuum:

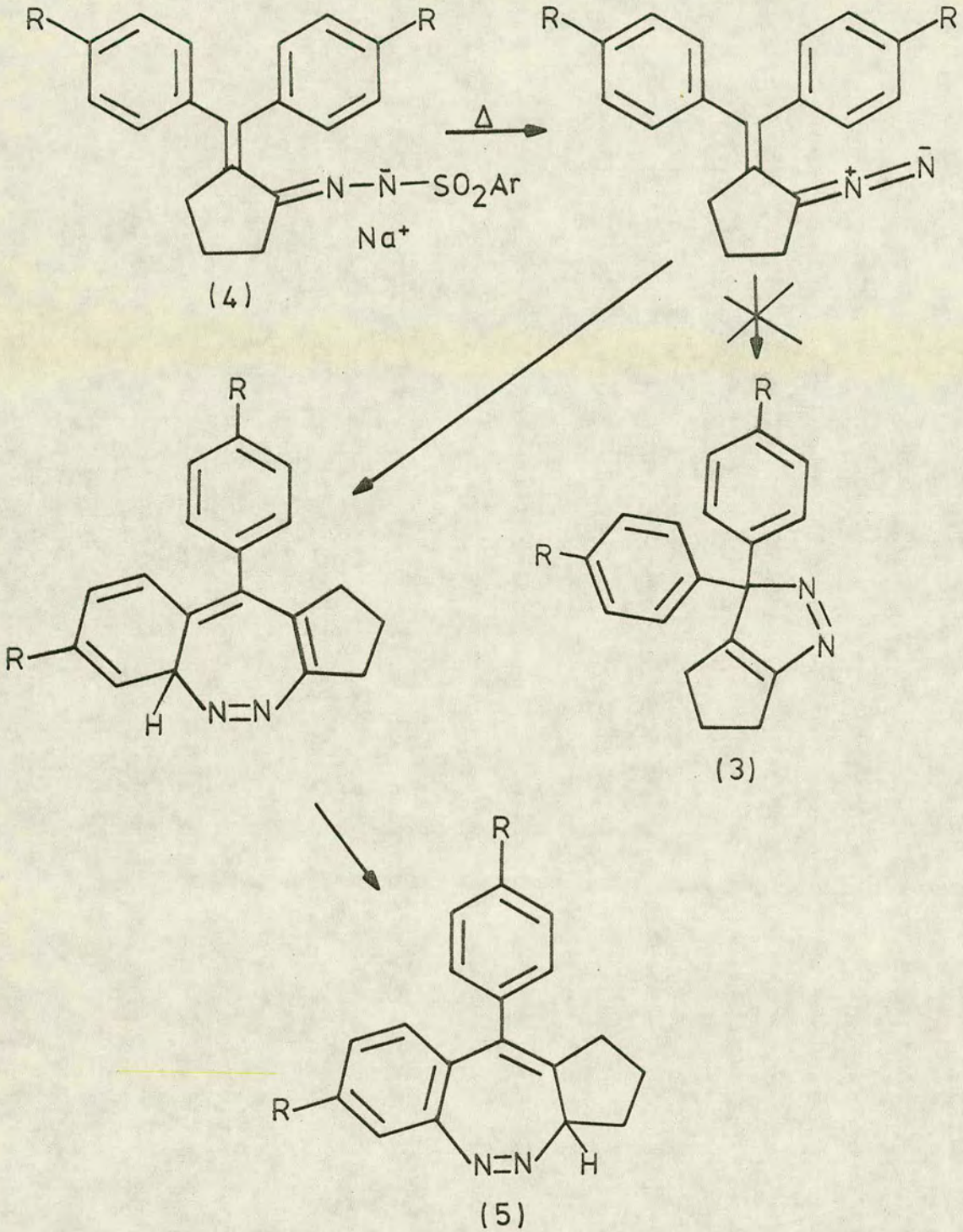


(1) (2)

a) $R=R^2=Me$, $R^1=H$ 36%

b) $R=Me$, $R^1R^2=-(CH_2)_5-$ 68%

The same workers showed that the 3H-pyrazoles, (2), readily eliminated nitrogen on photolysis to yield cyclopropenes:

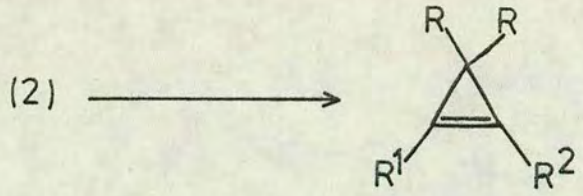


a) R = H, 80%

b) R = CH_3, 65%

c) R = F, 44%

Scheme (1)



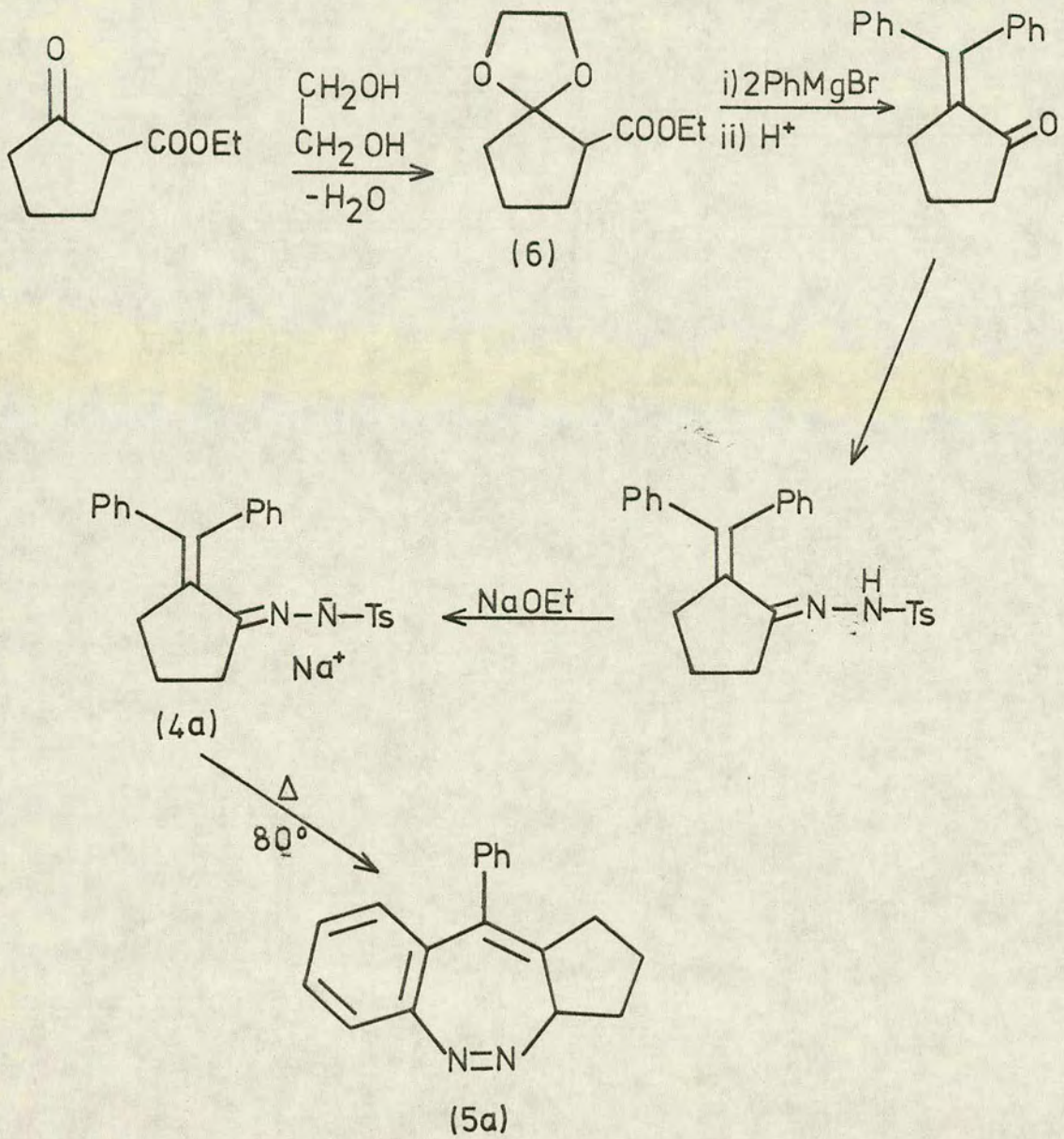
a) 65%

b) quant.

Recently, in a similar type of reaction, Sharp and co-workers[28], trying to prepare the pyrazoles (3) from the sodium salt (4) found instead that the previously unsynthesised 3H-1,2-benzodiazepines (5) were formed (scheme (1)). This novel cyclisation was explained by the steric inhibition of cyclisation on the double bond in (1) when R_1 and R_2 are members of the same cyclopentane ring. This makes attack of the intermediate diazocompound on the ortho-position of the adjacent benzene ring the more favoured mode of reaction, resulting in benzodiazepine formation.

Due to the current interest in the thermal and photochemical decompositions of acyclic and cyclic azocompounds*, this investigation began with a study of the thermal behaviour of (5a) especially with regard to the mechanism of decomposition. Preliminary examinations of the photolysis of (5) and its precursor (4a) have also been made.

* See Introduction.

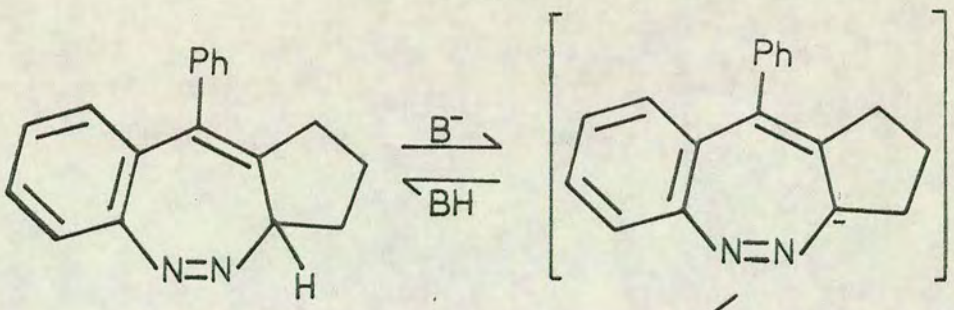

O
COOEt
CH2OH
CH2 OH
-H2O
O
O
COOEt
(6)
i) 2PhMgBr
ii) H+
Ph
Ph
O
Ph
Ph
N–N–Ts
H
Na+
NaOEt
(4a)
Δ
80°
Ph
N=N
(5a)

Scheme (2)

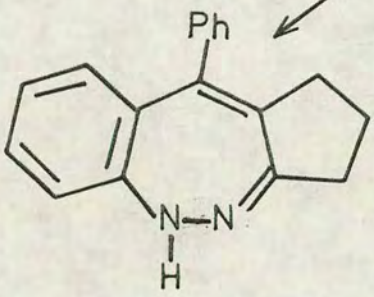
THERMAL AND PHOTOCHEMICAL REACTIONS OF 1,2-BENZODIAZEPINES AND THEIR PRECURSORS

I Preparation of 3H-1,2-Benzodiazepines

1,2,3,3a-Tetrahydro-10-phenylbenzo-[c]-cyclopenta-[f]-1,2-diazepine, (5a), was synthesised by the route outlined in scheme (2). Starting with 2-carbethoxycyclopentanone, the ketone carbonyl group was protected from Grignard attack by conversion to the ketal (6). The toluene-p-sulphonylhydrazone of 2-diphenylmethylenecyclopentanone was then prepared in the normal way by the acid-catalysed condensation of 4-toluenesulphonylhydrazide with the ketone. The careful execution of the next stage of the preparation is crucial for the success of benzodiazepine formation. Particular attention[98] must be paid to the base concentration used since any excess of base over toluene-p-sulphonylhydrazone results in the isomerisation of the product (5a) to the more stable 1H-isomer (7):



(5a)



(7)

For this reason, a 5% excess of toluene-p-sulphonyl-hydrazone was usually used. The sodium salt (4a) was formed by stirring 2-diphenylmethylenecyclopentanone toluene-p-sulphonylhydrazone in sodium ethoxide solution for twenty minutes at room temperature, and the ethanol was removed completely to leave the dry salt. This was achieved by evaporation of the ethanol on a rotary evaporator under reduced pressure at room temperature followed by dissolution of the sodium salt in dry, freshly-distilled 1,2-dimethoxyethane which was evaporated under reduced pressure again, to give the solid salt, which was now free from ethanol. This was then dried for at least 16h under high vacuum over fresh phosphorus pentoxide. The cyclisation step was then carried out by heating the sodium salt under reflux in dry, freshly-distilled 1,2-dimethoxyethane for four hours to give

1/...

Flash Vacuum Pyrolysis Apparatus

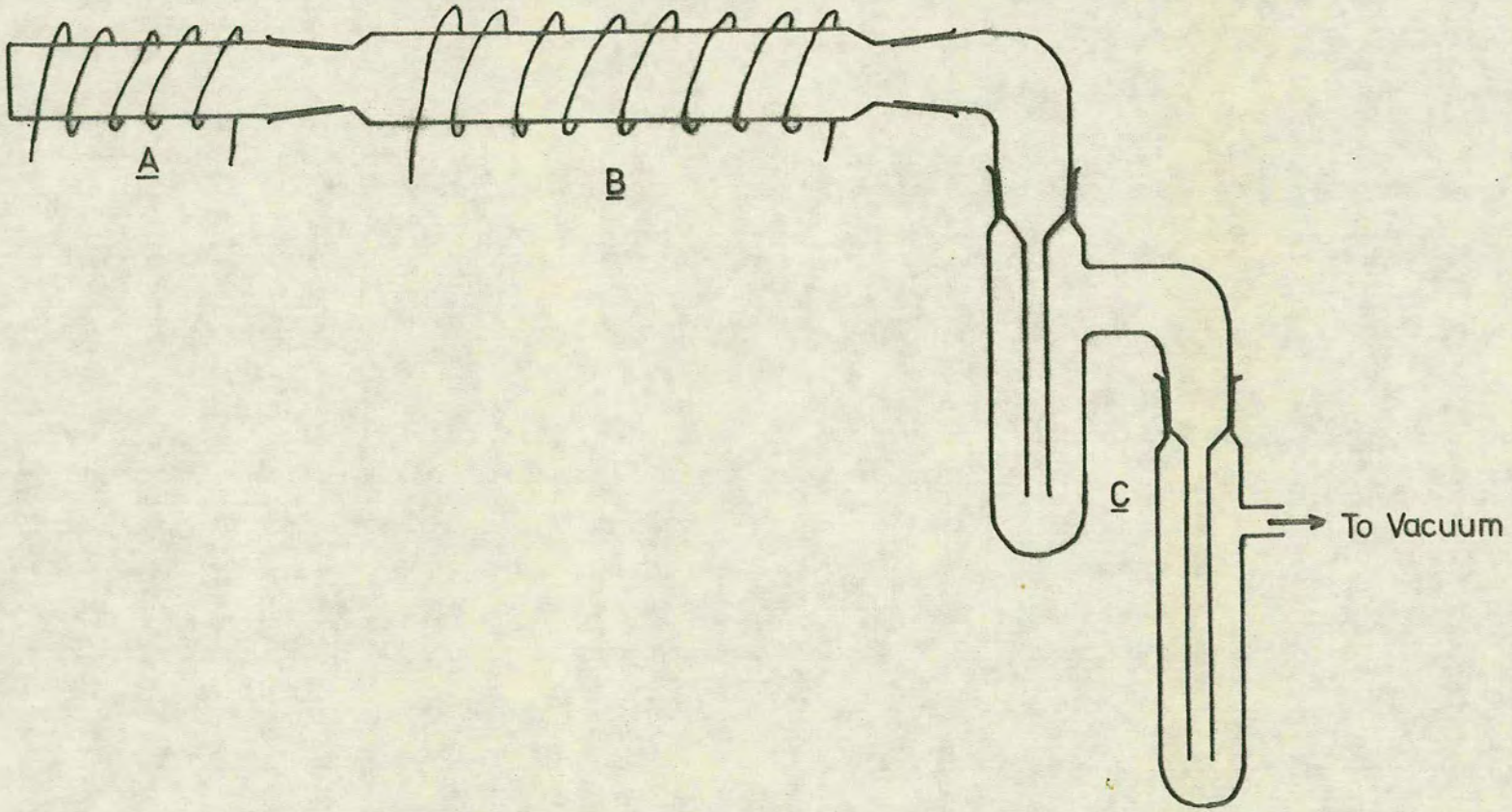


Fig. (i)

1,2,3,3a-tetrahydro-10-phenylbenzo-[c]-cyclopenta-[f]-1,2-diazepine in 80% yield.

1,2,3,3a-Tetrahydro-7-methyl-10-(p-tolyl)benzo-[c]-cyclopenta-[f]-1,2-diazepine was prepared in an exactly analogous manner, but using the Grignard reagent from p-bromotoluene rather than phenylmagnesium bromide. The yield in this case however was only 68%.

1,2,3,3a-Tetrahydro-7-fluoro-10-(p-fluorophenyl)benzo-[c]-cyclopenta-[f]-1,2-diazepine was similarly prepared in collaboration with Mr. G.M. Baird[97] as part of his Honours project.

The thermolysis of these benzodiazepines has been studied, in the gas phase, and at 111°-216° in various solvents.

II Gas Phase Decomposition of 3H-1,2-Benzodiazepines

The gas phase reactions were carried out in a vacuum pyrolysis apparatus of design[89] shown opposite (fig. (i)).

The sample inlet A consisted of a pyrex tube with a B19 socket joint at the inlet end and a B24 cone at the outlet to the furnace B which was made entirely from quartz, both ends consisting of B24 sockets. Both inlet and furnace were electrically heated, the former by a length of 0.024" nichrome wire of resistance 32ohms, and the latter/...

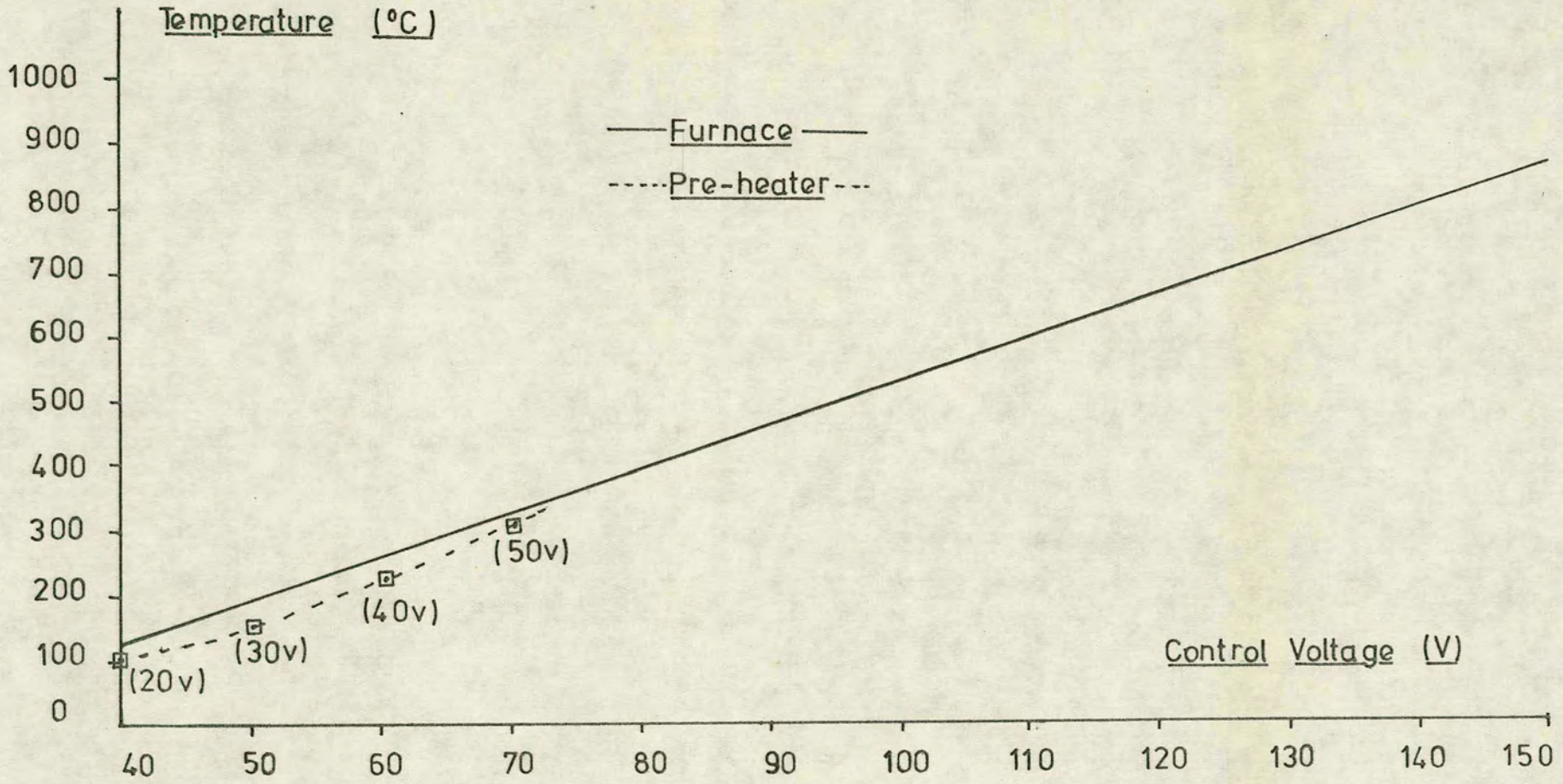

Temperature (°C)
1000
900
800
700
600
500
400
300
200
100
0
Furnace
Pre-heater
(20v)
(30v)
(40v)
(50v)
Control Voltage (V)
40
50
60
70
80
90
100
110
120
130
140
150

Fig. (ii)

latter by a length of similar wire of resistance 64ohms. In both sections, the wire turnings were insulated by winding with asbestos rope. Temperature calibration was then effected by measuring the temperature obtained for a given variac voltage using a chromel-alumel thermocouple and voltmeter, with a cold junction at 0°C. A plot of temperature against control voltage is shown in fig. (ii). This is consistent with the formula:[89]

$$T = (\frac{20V}{3} - 144)$$

over the range 40-60v, where T = temperature in °C and V = variac voltage.

The diazepine was initially placed in the sample inlet A and the whole apparatus was evacuated. Once a vacuum of 0.01 mm Hg had been obtained, the furnace, which was loosely packed with glass wool or quartz tubes, was allowed to equilibrate at the required pyrolysis temperature. The sample inlet heater was then switched on and its temperature adjusted to about 10° below the melting point of the compound being pyrolysed. This allowed for a slow sublimation of the benzodiazepine into the furnace where reaction took place. Reaction times were generally of the order 4-10h representing furnace contact times of the order of 10-100 milliseconds.[89]

The/...

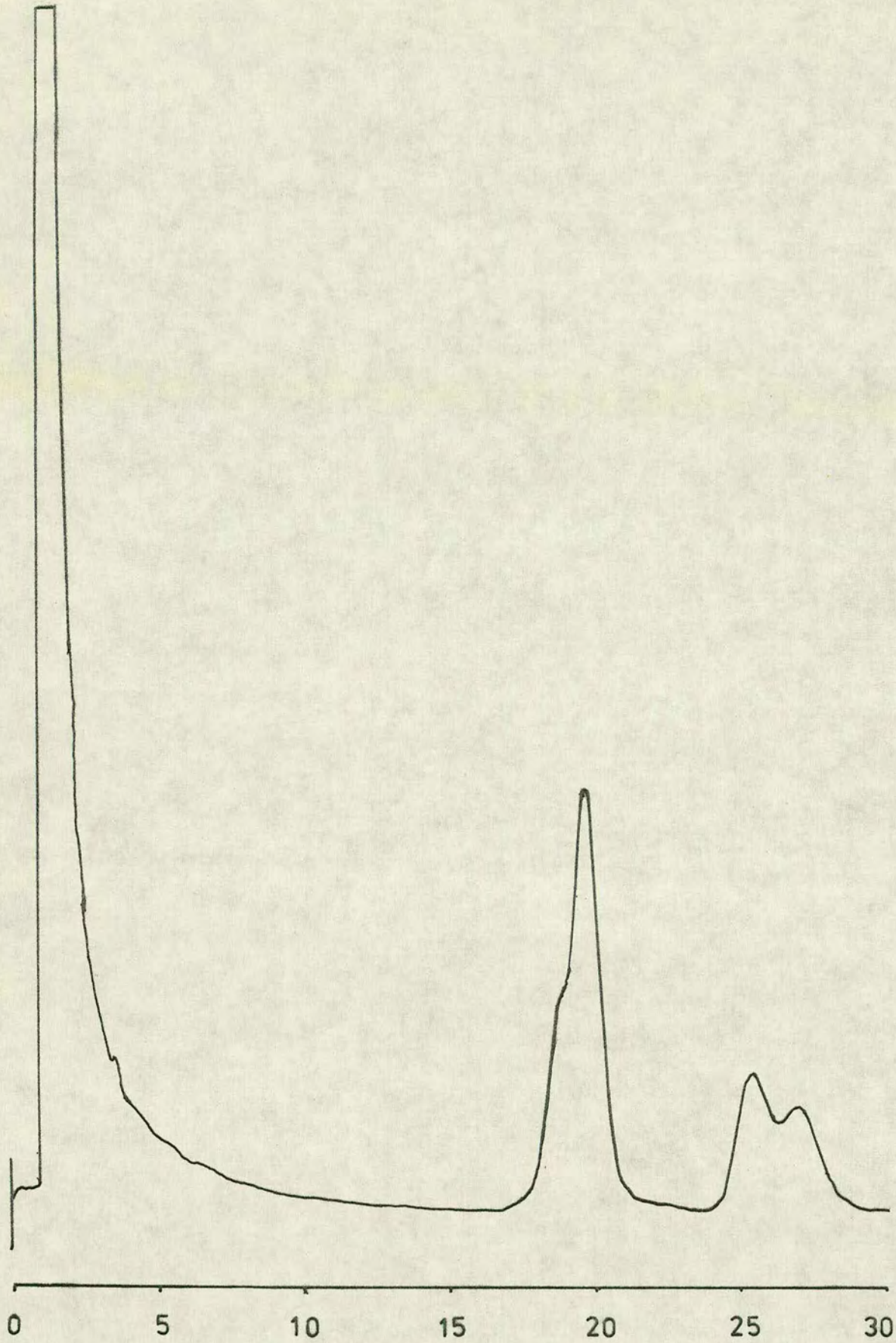
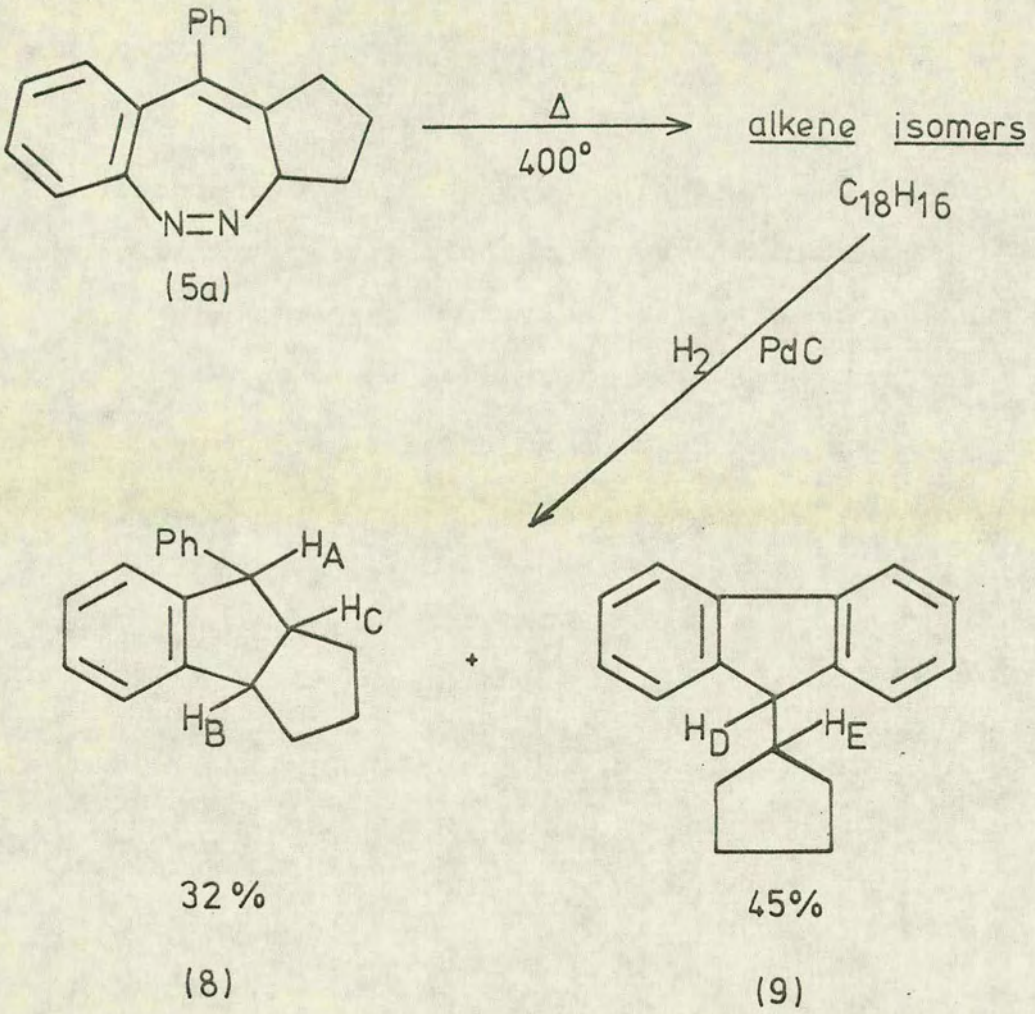


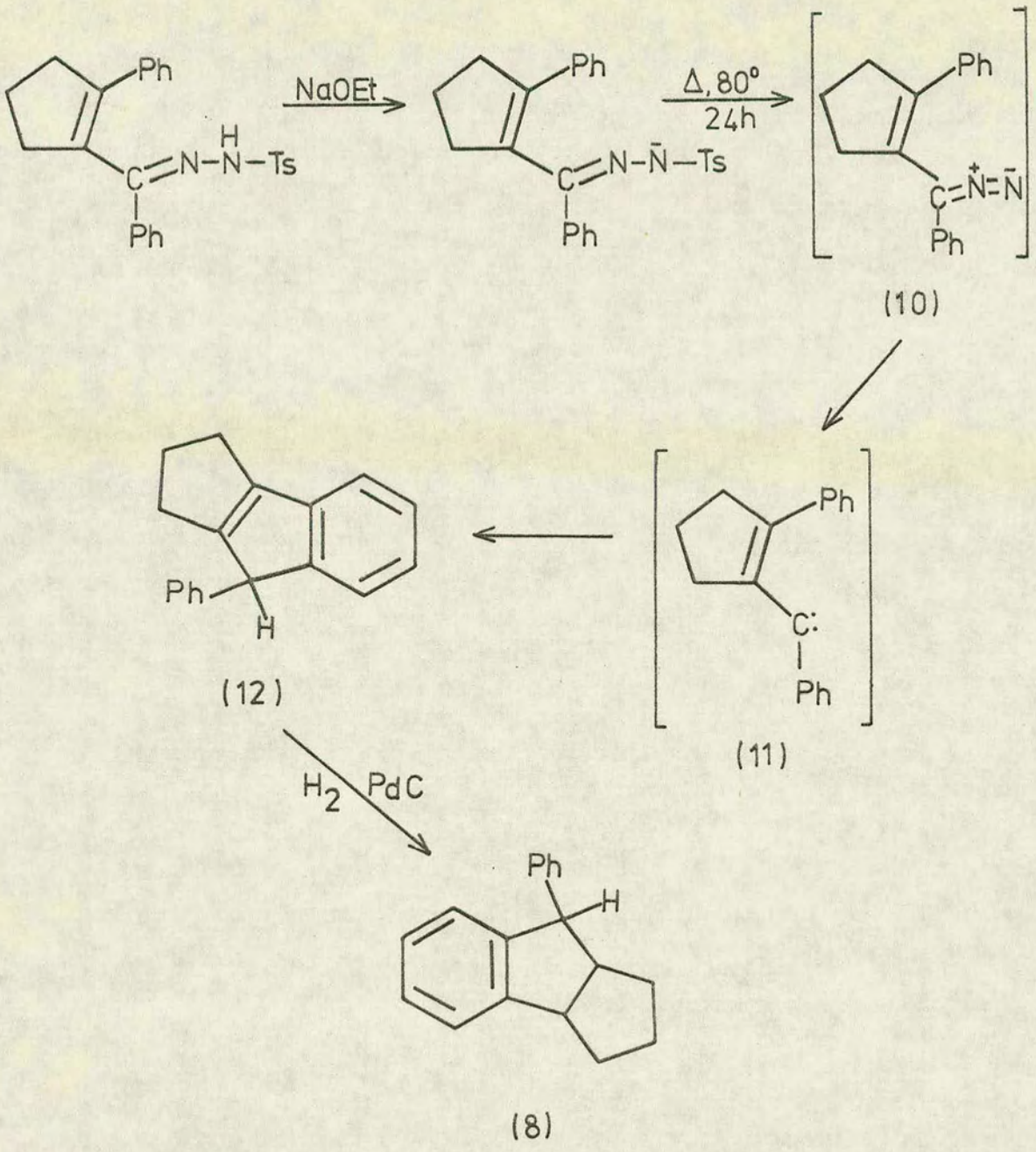
Fig. (iii)


Ph
N=N
(5a)
Δ
400°
alkene isomers
$C_{18}H_{16}$
H_2 PdC
Ph
H_A
H_C
H_B
H_D
H_E
32 %
(8)
45%
(9)

Scheme (3)

The products collected in the liquid nitrogen-cooled traps C from which they were quantitatively transferred to a flask with solvent (usually chloroform) which was evaporated under reduced pressure to give the products. Vacuum drying of the residue followed by weighing enabled yields to be calculated. The products were then identified by chemical and spectroscopic methods as discussed below.

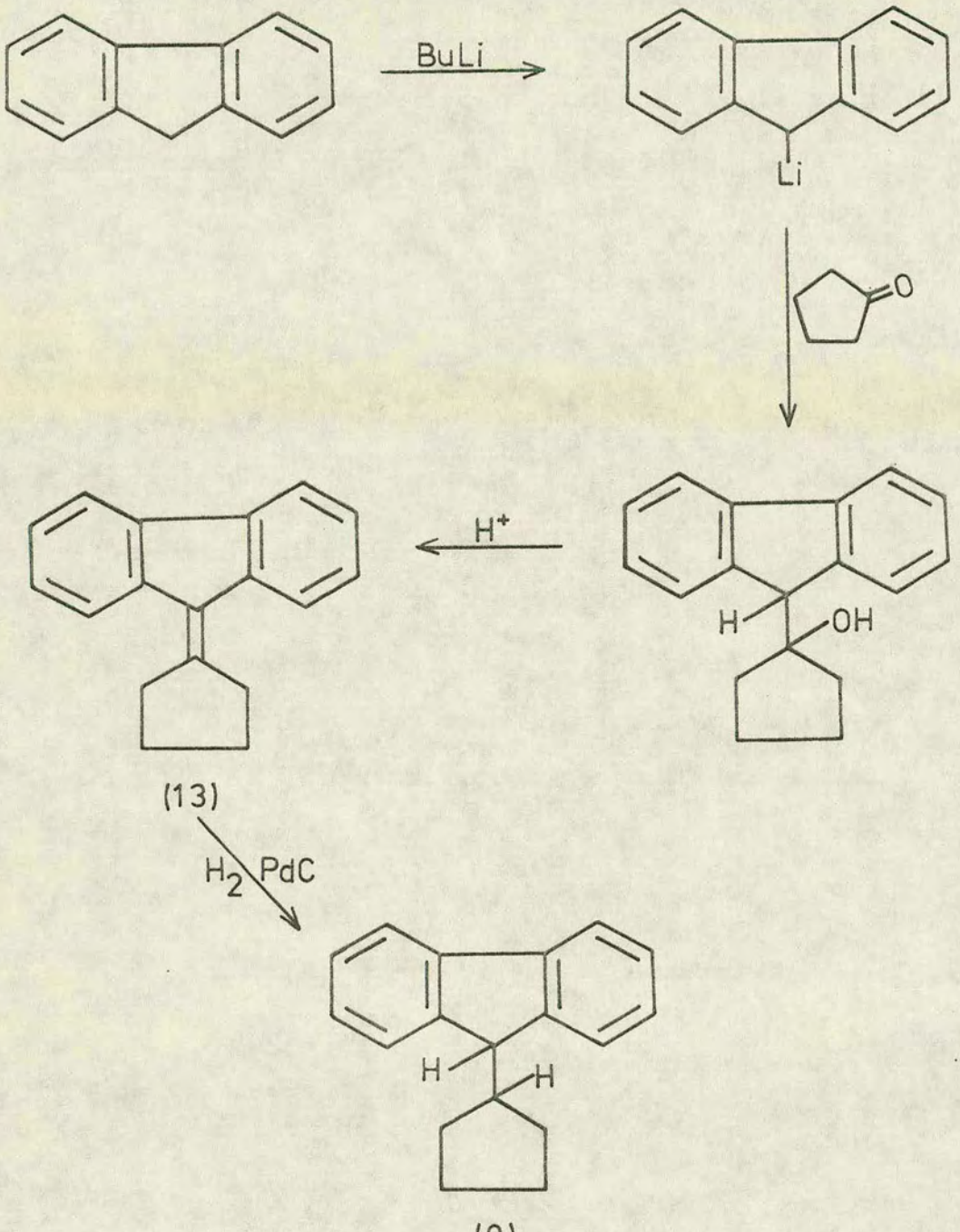
1,2,3,3a-Tetrahydro-10-phenylbenzo-[c]-cyclopenta-[f]-1,2-diazepine was pyrolysed in the gas phase as described above. To ensure that decomposition was taking place in the furnace and not in the inlet system, a control experiment in which the furnace was held at 200° while the inlet system was held at its usual temperature of 150°, was carried out. Under these conditions, the benzodiazepine passed through the furnace without significant decomposition, and was collected in high yield. At 400° however, complete decomposition with elimination of nitrogen occurred. GLC analysis (2½% OV1, 190°) of the product mixture showed four incompletely-resolved peaks (fig. (iii)), and glc coupled to [redacted] mass spectrometry showed that these represented isomeric compounds of molecular weight 232. These compounds proved to be inseparable by column chromatography. The mixture was therefore hydrogenated and gave a simpler mixture/...


Ph
NaOEt
H
N–N–Ts
Ph
Ph
Δ, 80°
24h
N–N̄–Ts
Ph
Ph
(10)
Ph
C:
Ph
(11)
Ph
H
(12)
H2
PdC
Ph
H
(8)

Scheme (4)

mixture of two isomeric compounds which were shown by glc/ms to have molecular weight 234. These products were found to be separable by column chromatography on alumina eluting with petroleum ether, and were assigned the structures (8) and (9) on the basis of their spectral and analytical data. These assignments were confirmed by comparisons with compounds prepared by alternative routes.

The nmr spectrum of (8) showed an aromatic multiplet at 2.9τ and a complex aliphatic multiplet between 7.6τ and 9.02τ, integrating for nine and six protons respectively. Besides these, there were three well-separated groups of lines: a doublet at 5.42τ (J = 8 cps), a triplet of doublets at 6.38τ (J = 8 cps, J' = 4 cps) and a quintuplet at 7.01τ (J = 8 cps) integrating for one proton each. The latter three resonances may be assigned to protons A, B and C in structure (8). Compound (8) was synthesised by the independent synthesis[98] outlined in scheme (4). The toluene-p-sulphonylhydrazone of 1-phenyl-2-benzoylcyclopentene was prepared in the usual manner, and from this, the sodium salt, which was dried in the normal way. The dried salt was decomposed in dry cyclohexane overnight. Reaction occurred *via* the diazocompound (10) which lost nitrogen to give the carbene (11) which in turn inserted into the o-position of the 1-phenyl substituent to give 1,2,3,8-tetrahydro-8-phenylcyclopenta-[b]-indene/...



Scheme (5)

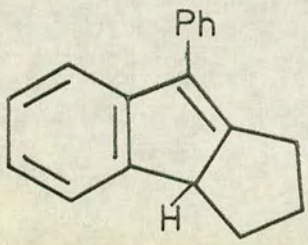
[b]-indene (12). The nmr spectrum of this compound is given in tabular form in appendix I.5. Hydrogenation of (12) then gave 3-phenylcyclopenta-[a]-indane which was identical in all respects to the compound (8) which was obtained from the pyrolysis-hydrogenation sequence.

The nmr spectrum of (9) showed three closely-spaced multiplets at 2.37τ, 2.58τ and 2.80τ in the ratio 2:2:4, which is consistent with an unsubstituted fluorene ring system, and a complex aliphatic multiplet between 8.1τ and 9.0τ integrating for eight protons which is consistent with a monosubstituted cyclopentyl ring. Besides these, there were also present a doublet at 6.08τ (J = 5 cps) and a multiplet at 7.66τ, integrating for one proton each. This spectrum is entirely consistent with the structure (9) proposed, the latter two resonances being assigned to protons D and E respectively.

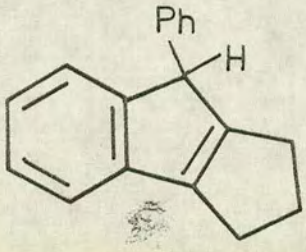
Authentic 9-cyclopentylfluorene was prepared by the independent route outlined in scheme (5). Alkylation of cyclopentanone with 9-fluorenyllithium followed by acid catalysed dehydration of the product gave 9-cyclopentylidenefluorene (13). The nmr spectrum of this compound is tabulated in appendix I.5. Hydrogenation of (13) gave 9-cyclopentylfluorene which was identical in every way to the compound (9) obtained from the pyrolysis-hydrogenation sequence.

Thus/...

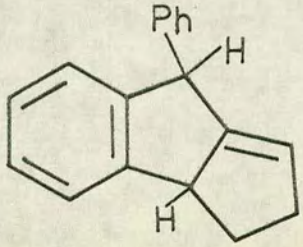
Alkene Isomers - $C_{18}H_{16}$



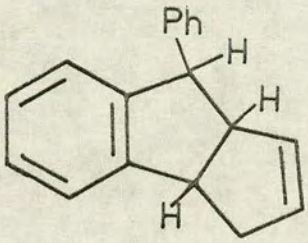
(14)



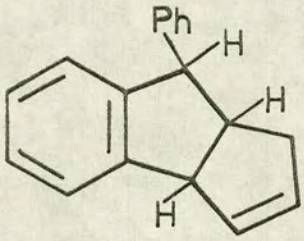
(12)



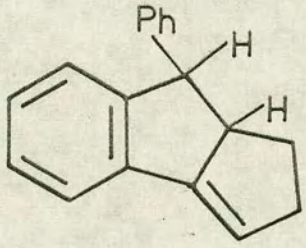
(15)



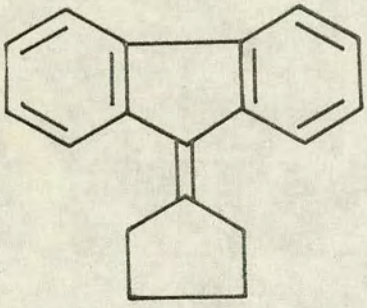
(16)



(17)



(18)



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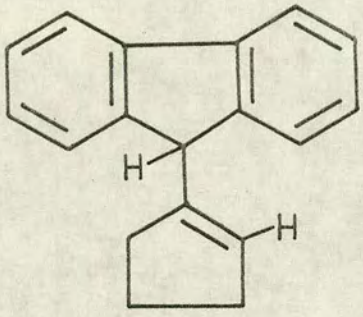
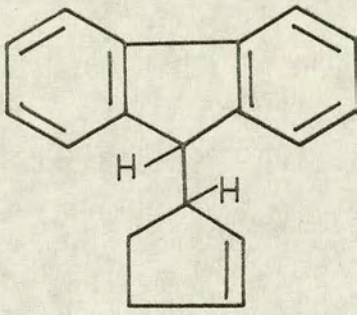
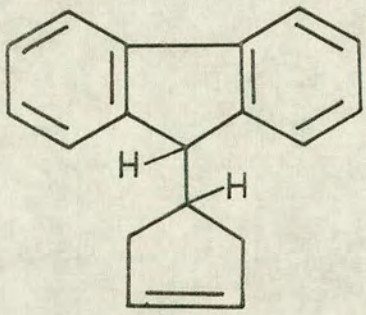


(19)



(20)



(21)

Thus, the mixture obtained from pyrolysis of (5a) at 400° in the gas phase gave (8) and (9) on hydrogenation by uptake of one molar equivalent of hydrogen for each compound present initially. This means that the pyrolysis products were isomers, the possible structures, (12)-(21), being shown opposite. The glc trace of the pyrolysate, (2½% OV1, 190°), however, showed only four peaks fig. (iii) suggesting the presence of only four compounds. The nmr spectrum of the pyrolysate is shown in fig. (iv). Each of the possible isomers should show some characteristic resonances, the presence or absence of which should indicate the constitution of the mixture. For example, (16) and (17) should show the same sort of patterns for the methine protons as does (8), whereas (18) should show a doublet at 6.5τ for the proton at the phenyl-substituted carbon atom, and (15) should show a triplet at about 6τ for the methine proton at the cyclopentane ring junction. Compounds (20) and (21) should show doublets at about 6τ for the 9-fluorenyl proton. None of these resonances were present (within the limits of detection of the nmr instrument i.e. about 1%) indicating that none of these compounds were present. By comparison of this nmr spectrum with that of 9-cyclopentylidene-fluorene (13), the absence of this compound was also confirmed. This leaves the three isomers (12), (14) and (19) in terms of which the nmr spectrum of the pyrolysate (fig. iv)) could be/...

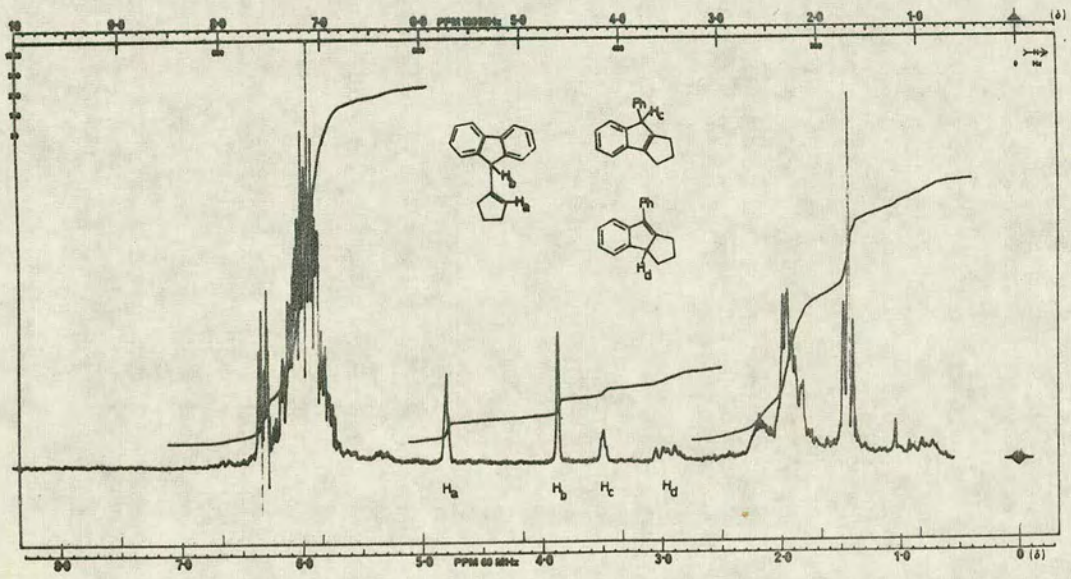
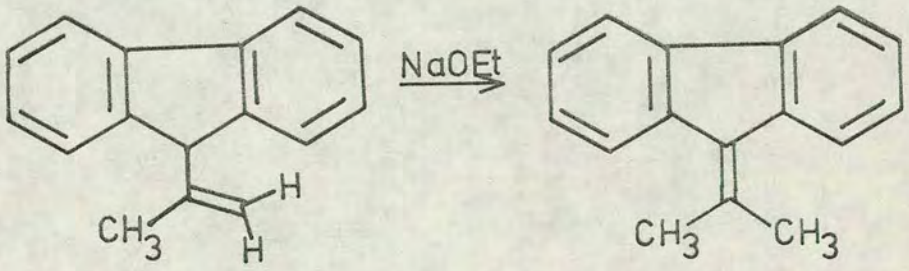


Fig. (iv)

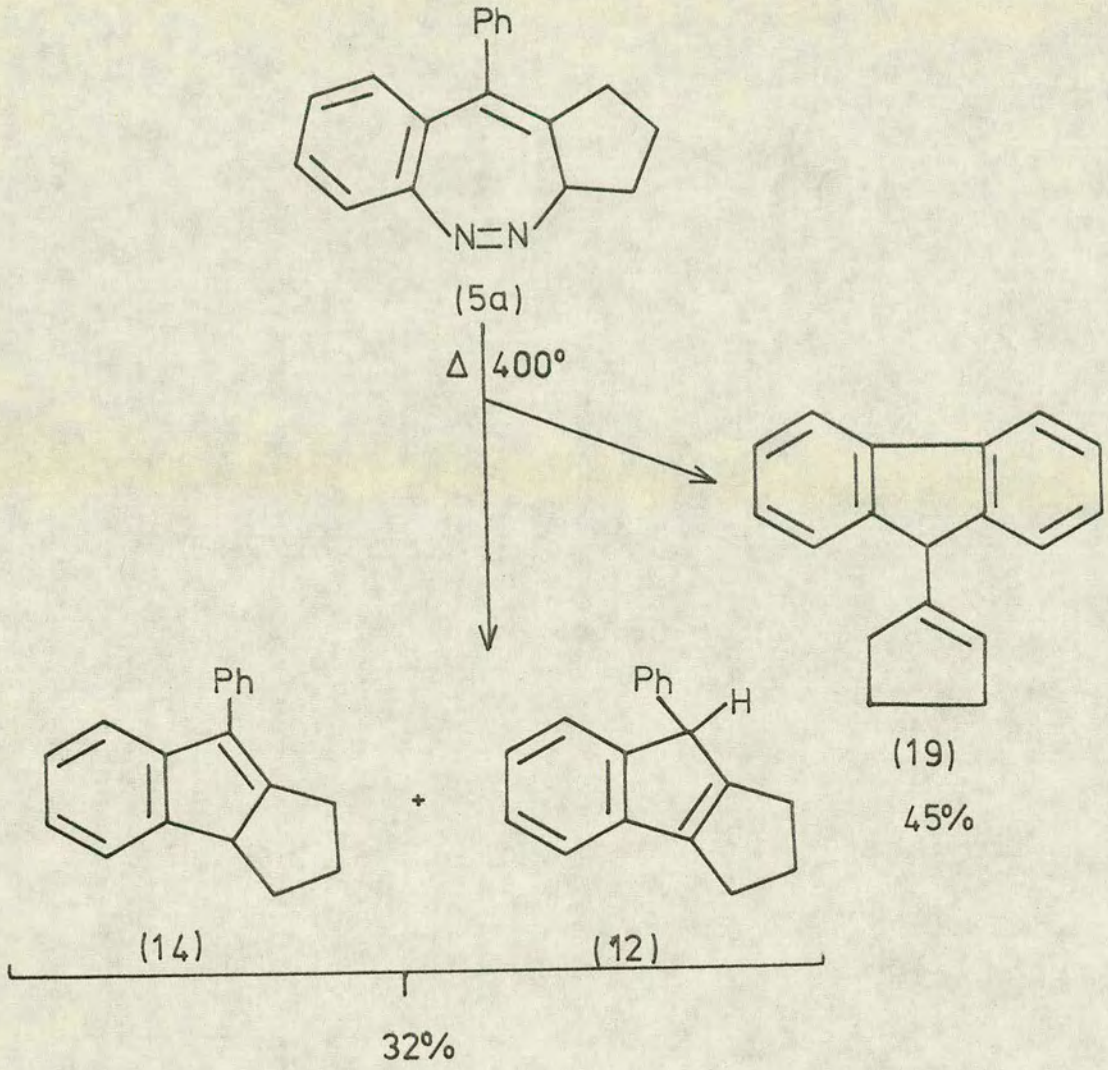
be explained. At 5.8τ was a broad, almost split singlet which was due to benzylic proton of (12), while at 4.26τ and 5.36τ were two broad singlets, again almost split, which can be assigned to the olefinic and 9-fluorenyl protons respectively in structure (19). Finally, there was a multiplet centred on 6.48τ which could be assigned to the benzylic proton in structure (14). Only (12) could be synthesised independently (scheme 4). The nmr spectrum of this compound showed the resonance at 5.8τ, (see appendix I.5), confirming the presence of (12) in the pyrolysate.

Further evidence for the presence of (19) may be drawn from the analogous system (22) prepared by Stewart:[99]

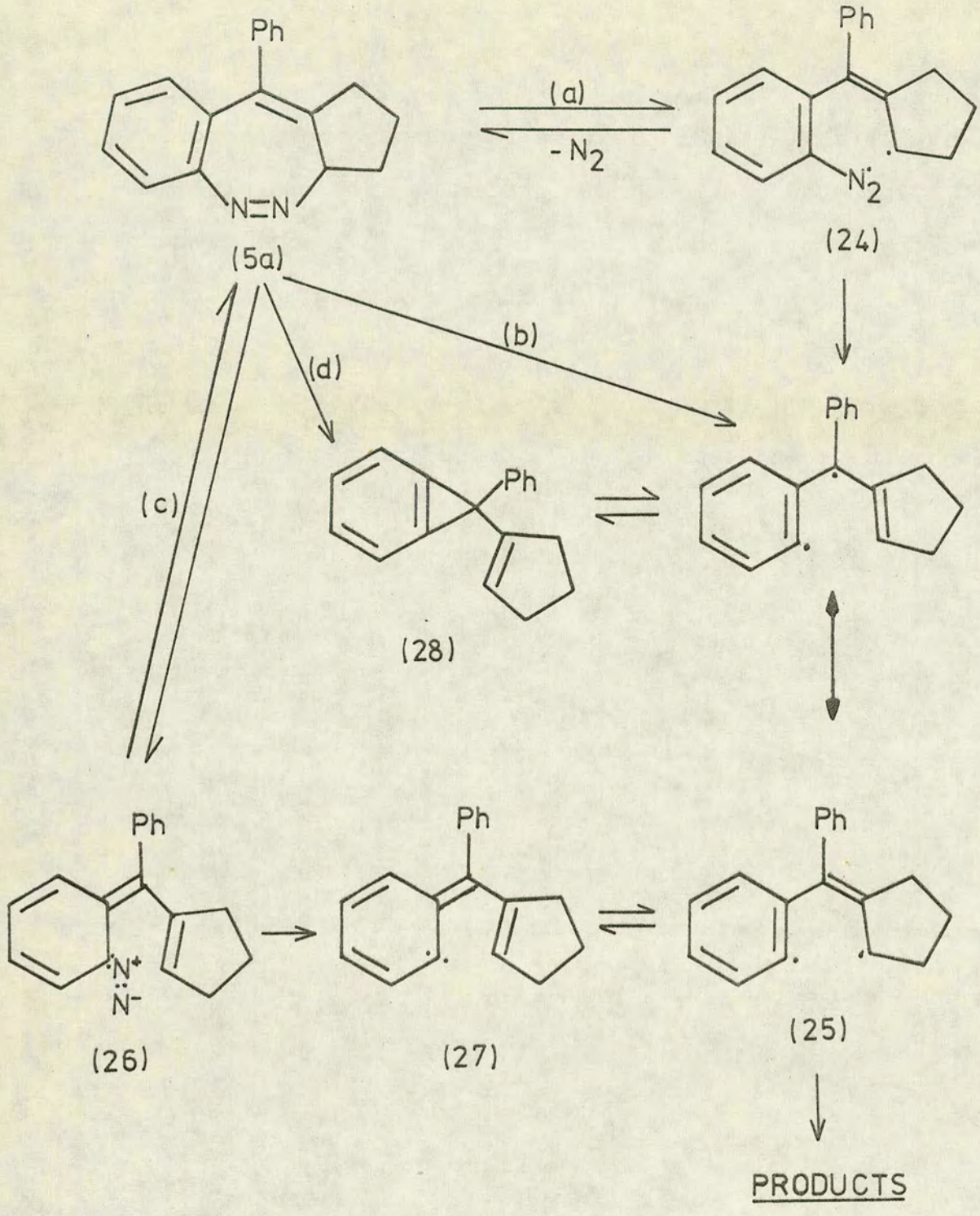


(22) (23)

Compound (22) showed resonances at 5.50τ for the 9-fluorenyl proton and at 4.98τ and 4.76τ for the olefinic protons, which are similar to the resonances interpreted as the corresponding protons of (19). Furthermore, when/...



Scheme (6)

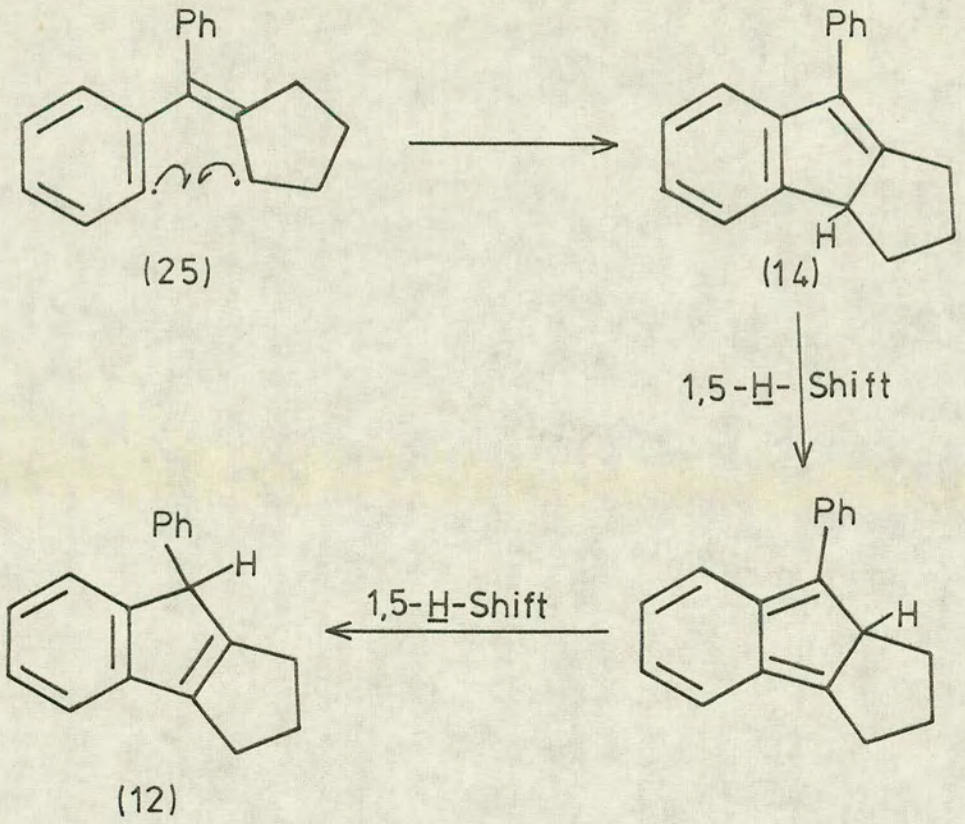


Scheme (7)

when (22) was allowed to stand in sodium ethoxide solution overnight, the double bond migrated to form the more stable 9-isopropylidene isomer (23). In a similar manner, treatment of pyrolysate with sodium ethoxide solution resulted in loss of the resonances at 4.26τ and 5.36τ with concurrent appearance of aliphatic multiplets at 7.0τ and 8.1τ which were identical to those of authentic 9-cyclopentylidenefluorene. The presence of the latter was confirmed by glc (1% SE30, 170^{o}). The only evidence for the presence of (14) in the pyrolysate is the multiplet resonance at 6.48τ, but this seems a reasonable interpretation of this part of the nmr spectrum. The fourth peak in the initial glc of the pyrolysate remains unexplained, but is possibly due to partial isomerisation of one of the compounds (12), (14) or (19) in the glc injection port or on the column. It must also be noted here that neither (12) nor (13) (nor indeed a third isomer, 3-(diphenylmethylene)cyclopentene*) were isomerised on pyrolysis at 400^{o} or prolonged hydrogenation at up to eight atmospheres pressure. Taken together, these results indicate that (12), (14) and (19) are the major primary products of the decomposition whereas (13) is definitely absent (scheme 6).

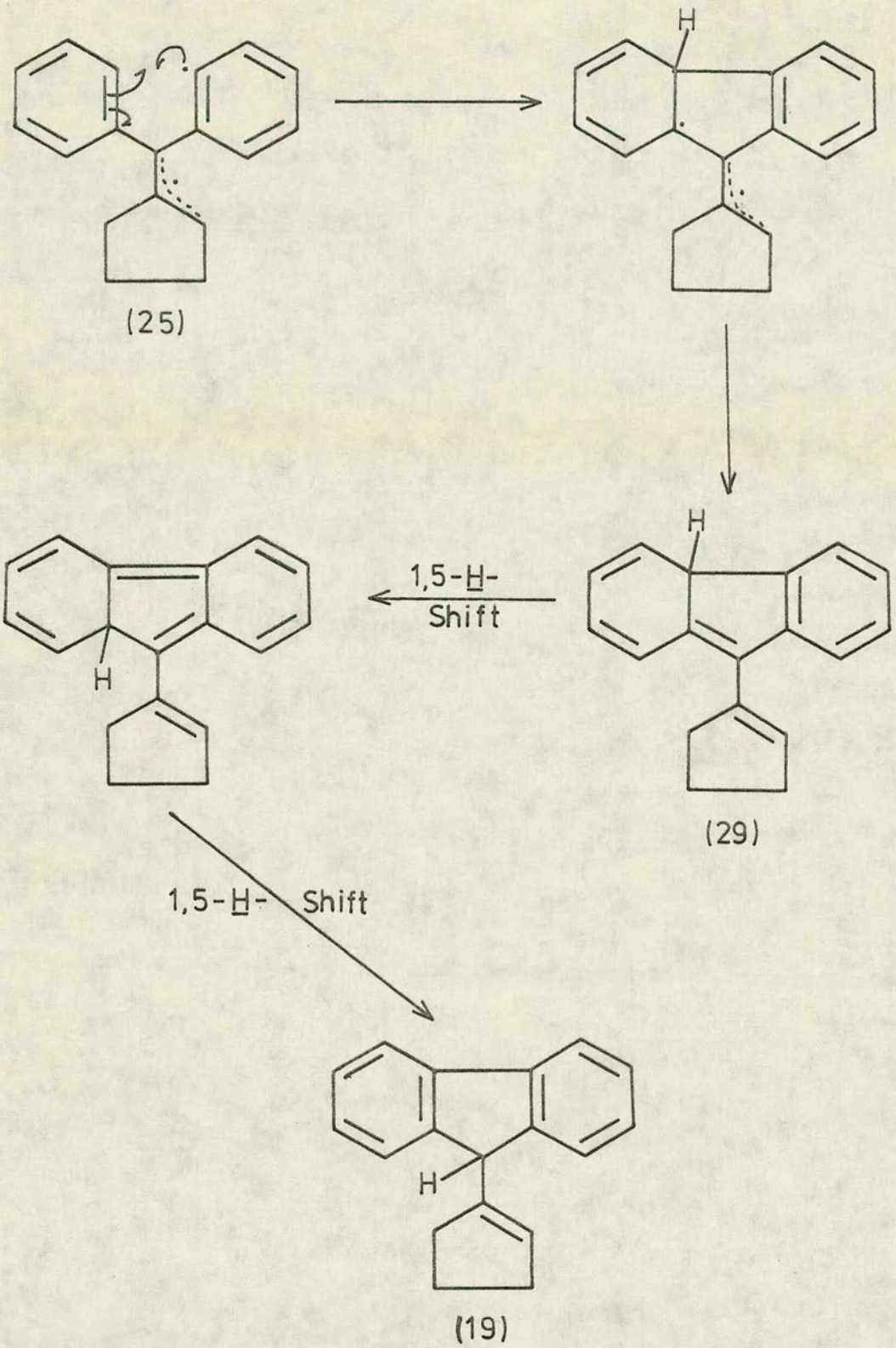
Four mechanistic possibilities for the reaction are shown in scheme (7). These are:

* See section III below



(25) (14) (12)

Scheme (8)



Scheme (9)

a) a one-bond scission mechanism leading to the nitrogen-containing diradical (24) which goes on to form the diradical (25);

b) direct extrusion of nitrogen by "two-bond scission" to form the diradical (25);

c) electrocyclic ring-opening to give the diazocompound (26) which reacts by nitrogen-loss to give the carbene (27) which then itself undergoes conversion to the diradical (25);

d) loss of nitrogen with concerted formation of the benzocyclopropene intermediate (28) which could in turn ring open to give the diradical (25).

The intermediate (25) could then react by radical combination to give the cyclopentaindene product (scheme 8) or by radical substitution of the substituted phenyl radical centre into the o-position of the other benzene ring to give the fluorene product (scheme 9). Scheme (8) shows why both (12) and (14) might be formed while scheme (9) shows why (19) is formed rather than the more stable isomer, 9-cyclopentylidenefluorene. In the latter case, assuming reaction via the intermediate (29), then a 1,5-sigmatropic hydrogen migration from the hexadiene ring junction to the 9-cyclopentane ring would be forbidden thermally, allowed 1,5-shifts being as shown.

Of the four possibilities for diradical formation, route (c)/...

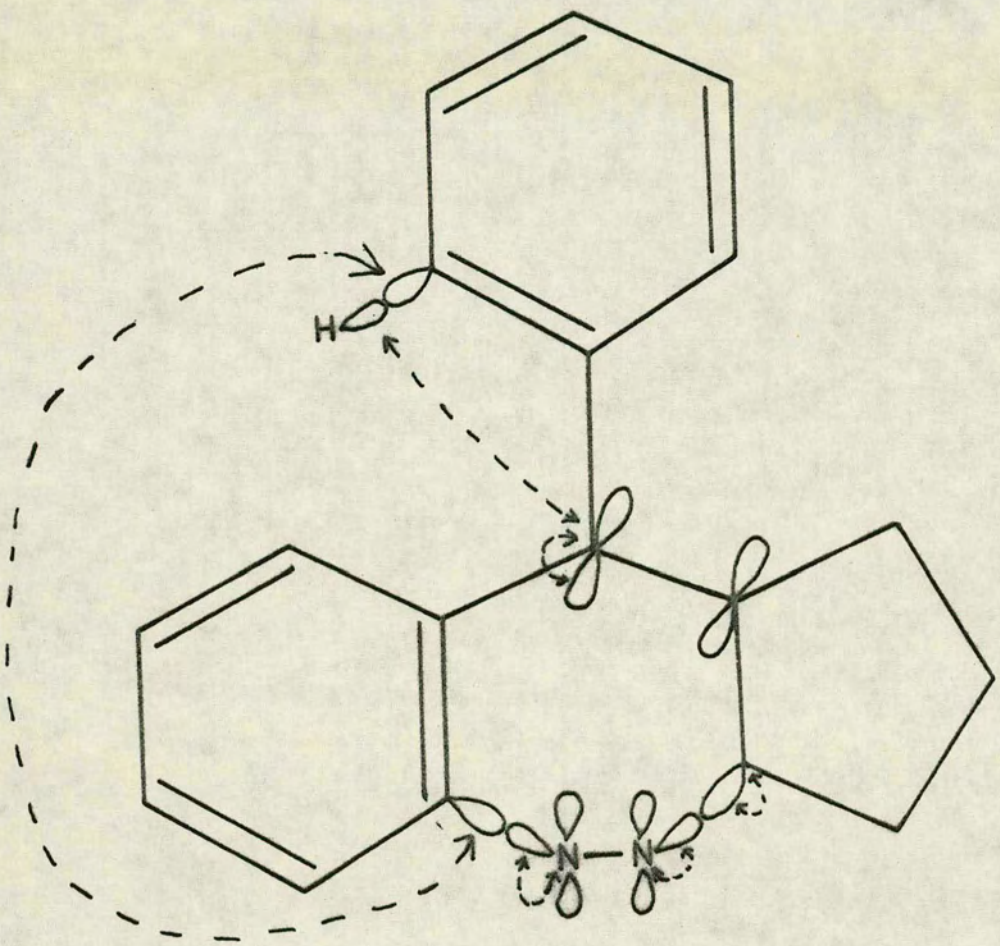


Fig. (v)

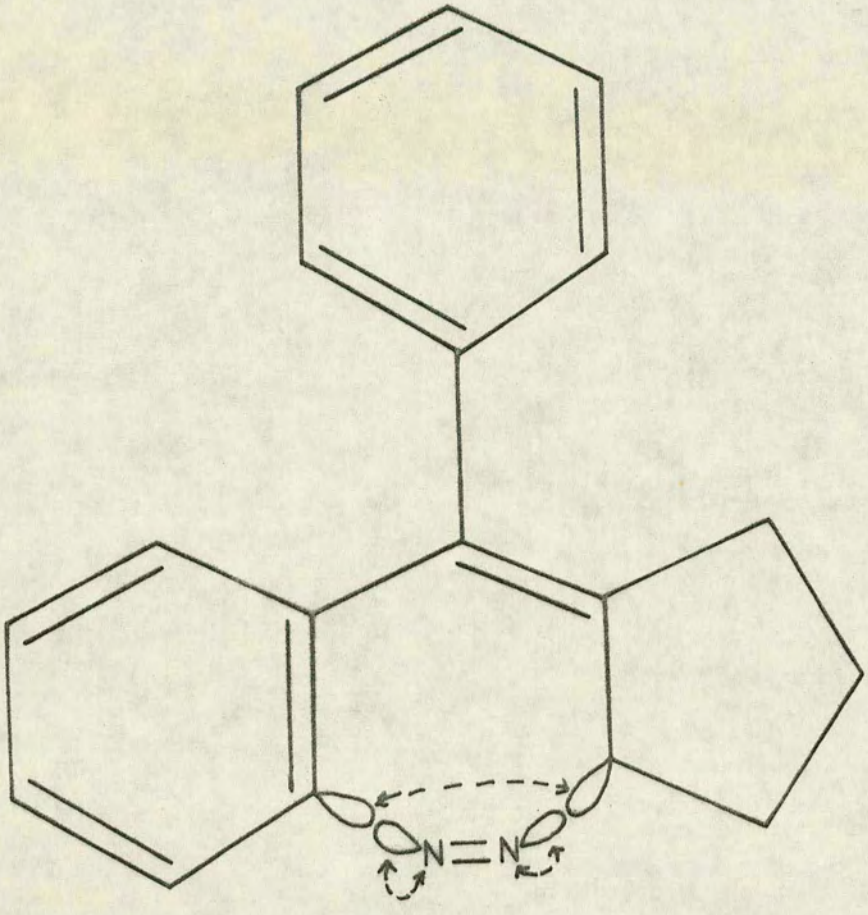


Fig. (vi)

(c) seems the most unlikely since the aromatic stability of a benzene ring must be disrupted to form the diazo-compound (26). It is, however difficult to differentiate between (a) and (b), but it seems likely that the weaker bond, the aliphatic carbon-nitrogen bond, fragments first to give the more stable allyl radical, and this is followed closely by scission of the second carbon-nitrogen bond to give (25), and hence the products. It should be noted here that the products (12), (14) and (19) cannot be formed from the benzodiazepine in concerted processes. In the latter case this is due to the impossible geometry which would be required in the transition state (fig. (v)). In the former case, the transition state may be represented by fig. (vi). The only interactions involved in moving to the product are the two σ-interactions shown, both of these retaining the configuration at both ends of the bond concerned - so-called suprafacial interactions. In the Woodward-Hoffmann[100] notation, both of these are σ_{2s} components since two electrons are involved in two σ-orbitals. Now, Woodward and Hoffmann state the general selection rule for pericyclic reactions as follows:

"A ground state pericyclic change is symmetry-allowed when the total number of (4q+2) suprafacial and 4r antarafacial components is odd", (q and r being zero or integers).

The/...

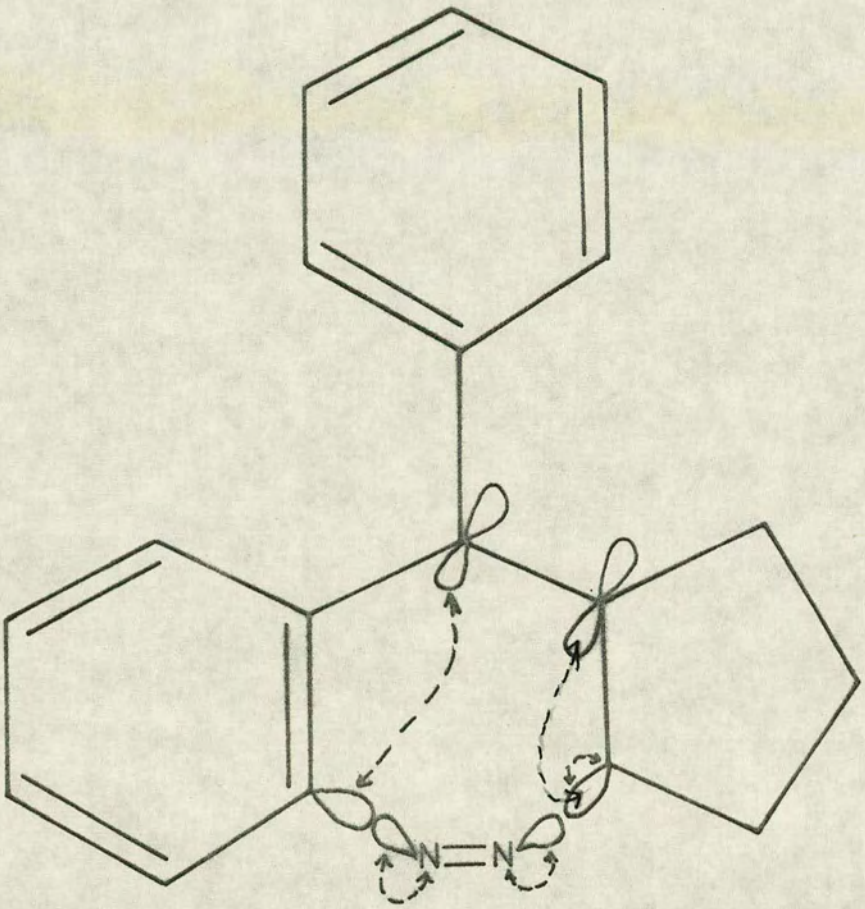
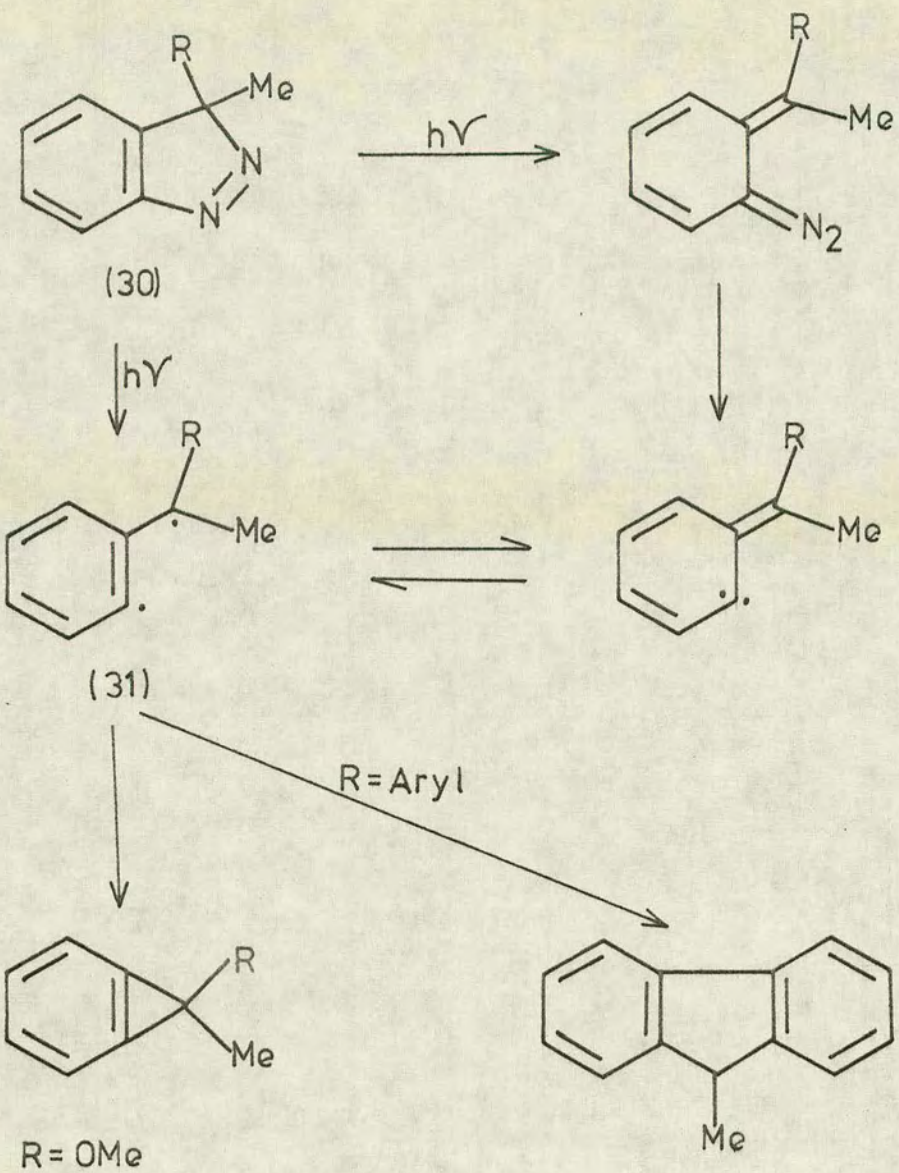


Fig. (vii)

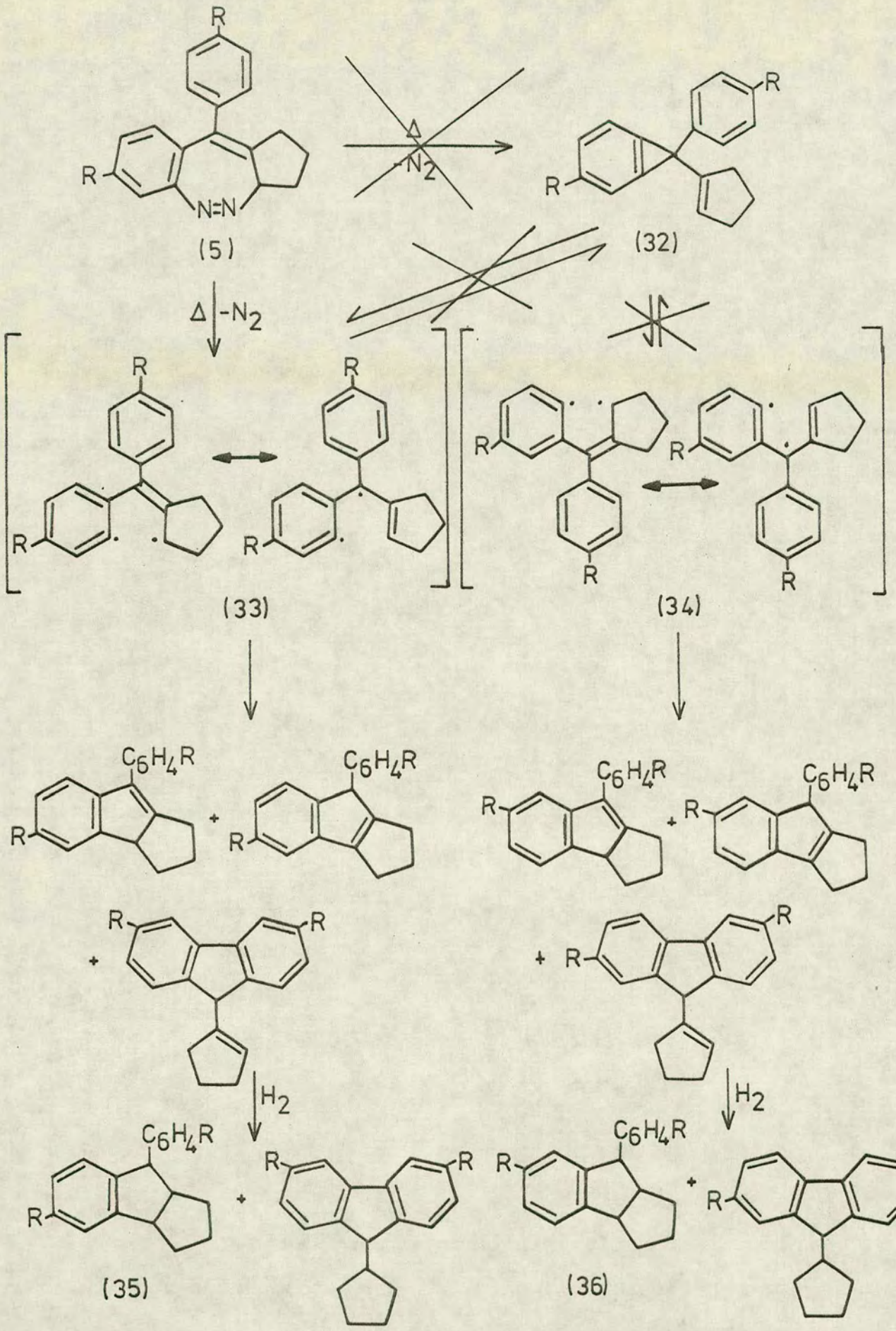


Scheme (11)

The total (4q+2) electron suprafacial components are the two σ2s interactions described above, there being no 4r antarafacial components. Thus, the total $(4q+2)_s$ + $(4r)_a$ components is 2 which is an even number and hence, the transformation of (5a) into (14) is symmetry-forbidden in a thermal process.

Howevever, a concerted route to the benzocyclopropene (28) is possible via the transition state shown in fig. (vii). Here, there are two σ2s components and one π2s component all being $(4q+2)_s$ components. There are no $(4r)_a$ components. Thus, the total $(4q+2)_s$ + $(4r)_a$ components is 3 which is an odd number, implying that this transformation is symmetry-allowed in a thermal process. This means then that (28) may be the primary product of reaction and that this transient intermediate ring-opens to (25) with subsequent formation of the observed products (scheme 7(d)).

It has been shown[101] that the 3H-indazoles (30) give benzocyclopropenes on photolysis (scheme 11). The first authenticated report of this type was by Anet and Anet[102] in 1964 and the method has subsequently been developed by Closs[103] and his coworkers. When the group R is an aryl ring, no benzocyclopropene is formed, but instead, a fluorene derivative, presumably via the diradical intermediate (31). However, there has been no/...



b) R= CH_3 c) R= F

Scheme (12)

noreport of a corresponding thermal reaction.

In view of this, and the possibility of a concerted route to the benzocyclopropene (28) from the benzodiazepine (5a), it was decided to investigate the possible intermediacy of a benzocyclopropene in the decomposition at hand. A convenient test for this possibility would be a product study of the decomposition of the substituted benzodiazepines (5b) and (5c). If the benzocyclopropene (32) were formed, then it could ring-open in two distinct ways to form two different diradicals (33) and (34), and hence two distinct sets of products as outlined in scheme (12). A study of the diazepines (5b) and (5c) was therefore undertaken, and it was hoped to differentiate between the isomeric products by glc and/or nmr spectroscopy.

At 400° in the gas phase, 1,2,3,3a-tetrahydro-7-methyl-10-(p-tolyl)benzo-[c]-cyclopenta-[f]-1,2-diazepine (5b) underwent an analogous elimination of nitrogen to that observed for the unsubstituted compound. Once more, glc analysis (2½% OV1, 200°) showed only four peaks suggesting four compounds. GLC coupled to high resolution mass spectrometry showed these to be isomers of molecular weight 260. The pyrolysate was hydrogenated, and, as before, the initial complex mixture was reduced to one of apparently only two compounds as shown by glc (2½% OV1, 200°)/...

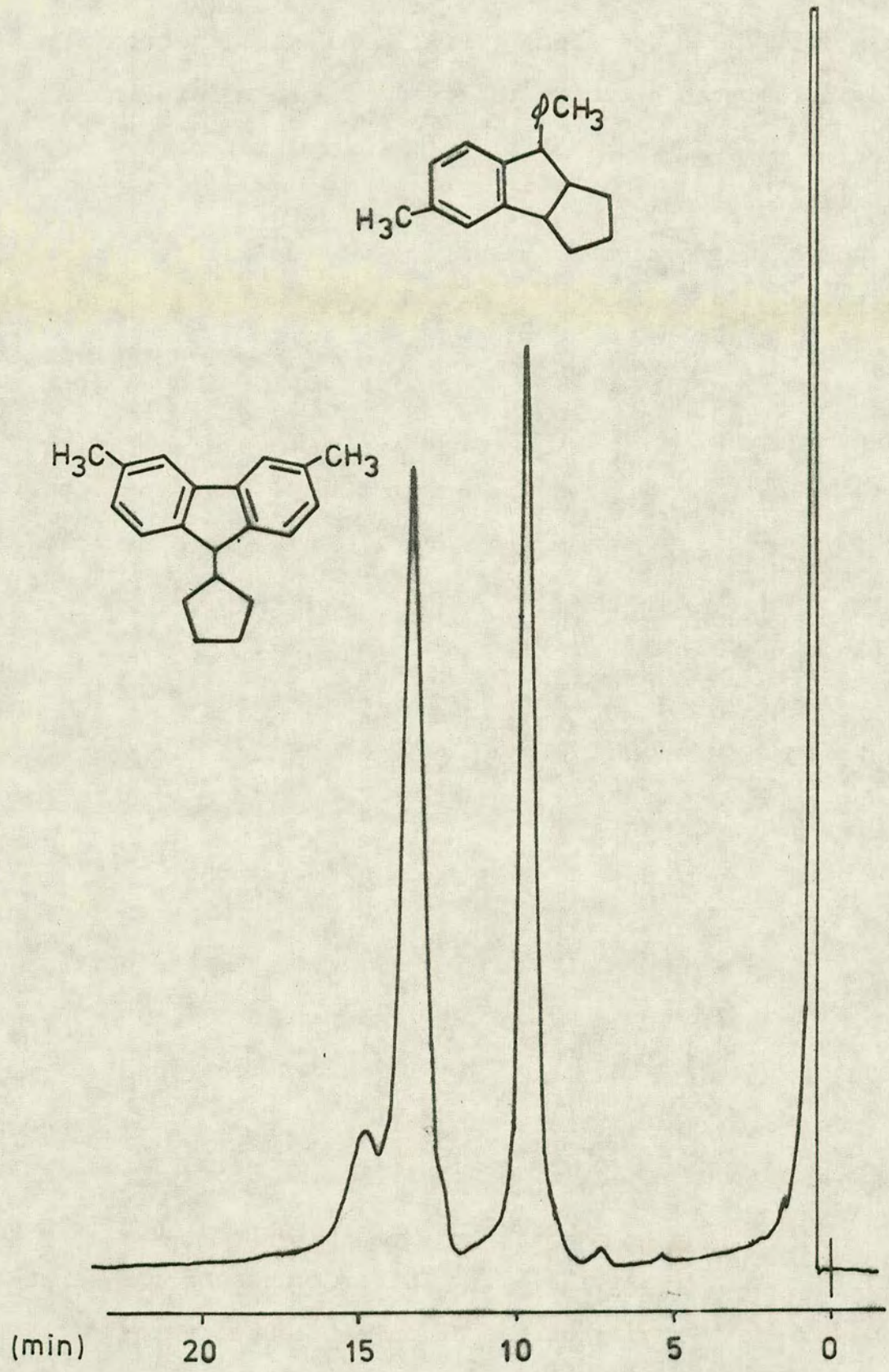
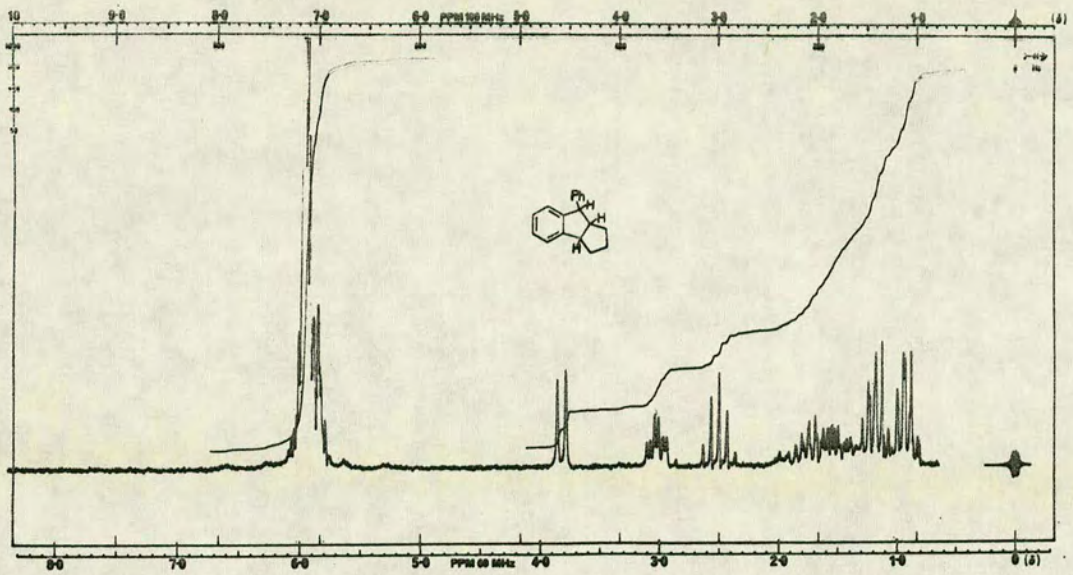


Fig. (viii)

(2½% OV1, 200°) see fig. (viii). GLC-mass spectrometry showed that the hydrogenated products had molecular weights of 262 which again, is analogous to the unsubstituted compound. The mixture was separated by column chromatography on alumina, eluting with petroleum ether, and the purified compounds were assigned structures on the basis of their spectral and analytical data, and by analogy with the unsubstituted case.

Once again, the nmr spectra of the hydrogenated products proved to be invaluable in their structure determination. These spectra are shown in figs. (ix) and (x) along with the spectra of the unsubstituted products. For the cyclopentaindane structure, the substitution of two methyl groups had little effect on the aliphatic part of the spectrum apart from the additional resonance at 7.7τ due to these methyl protons. However, the aromatic region was greatly simplified, only three lines in the ratio 4:1:2 being present. Unfortunately, this pattern can be fitted to either of the structures (35b) or (36b), but the sharpness of the lines throughout the spectrum suggested that only one compound was present. On the other hand, the spectrum of the fluorene product, also simplified by methyl substitution, can be assigned to a unique structure viz (37b). The broadness of the singlet at 2.59τ is very suggestive of only m-coupling to another proton/...



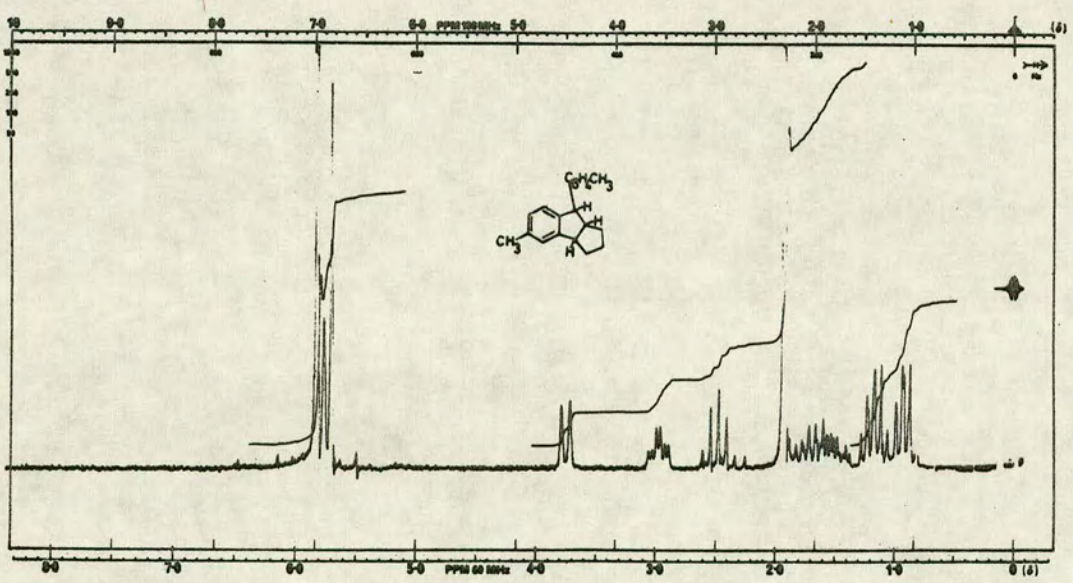
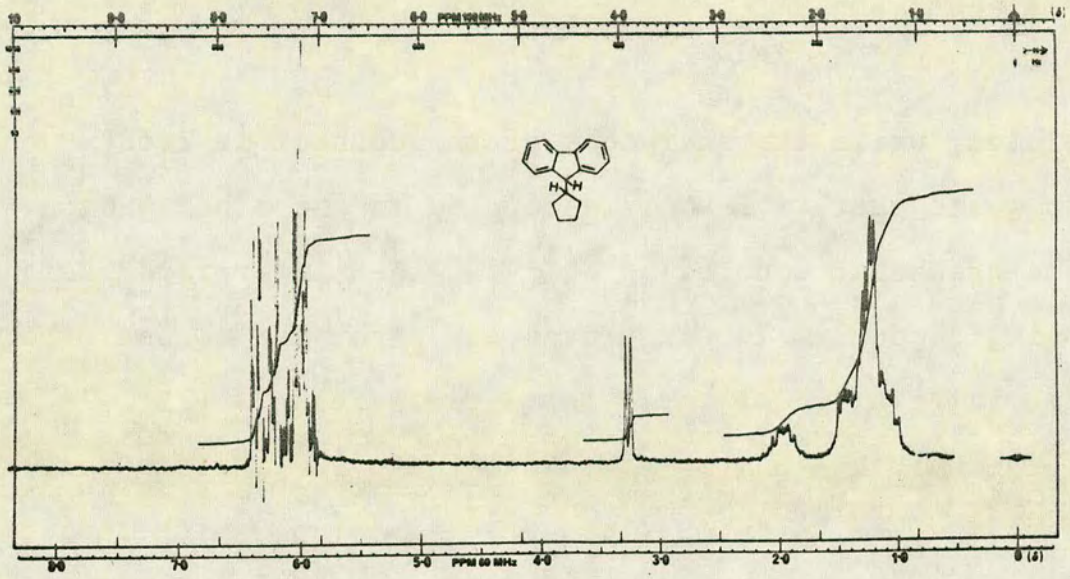


Fig. (ix)



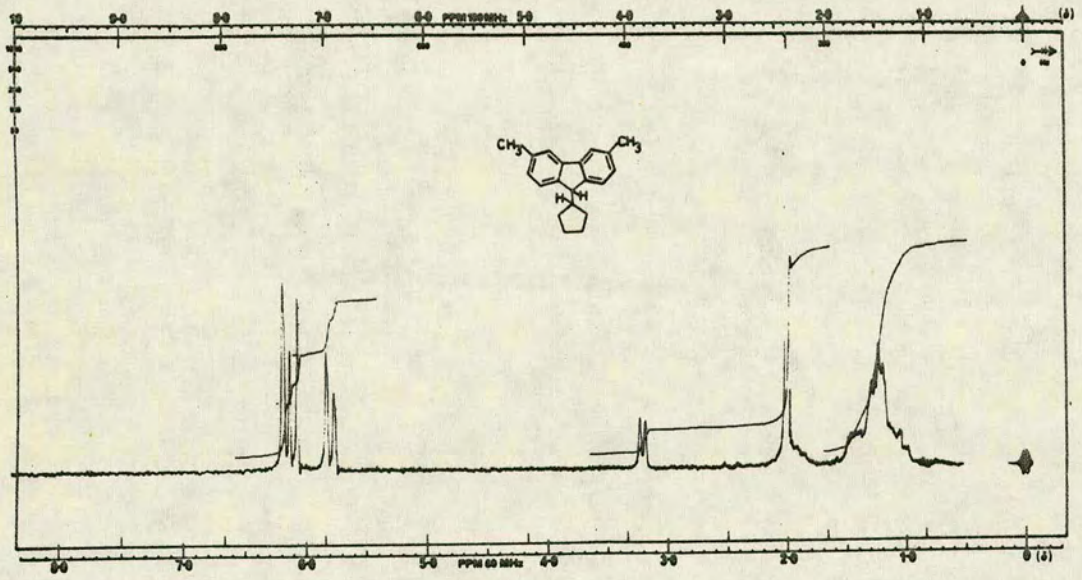


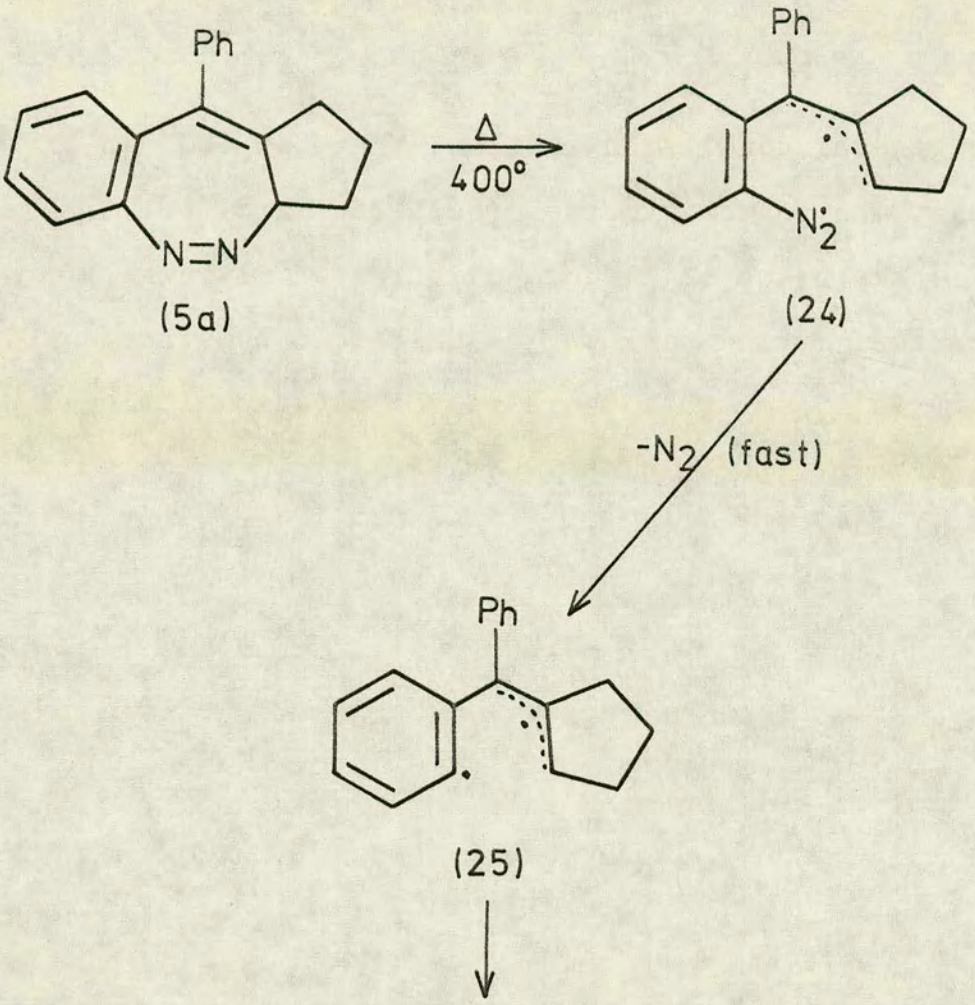
Fig. (x)

proton, while the sharpness of the doublet at 2.68τ suggests that it is only o-coupled to one other proton. The broadened doublet at 3.25τ is then interpreted as being o-coupled to one proton and m-coupled to one other. The integration of these three resonances is 1:1:1. These data can only be accommodated by a fluorene ring system which is symmetrically substituted, which implies structure (37b) in this case. The fact that there are no overlapping groups of lines and only a single methyl resonance strongly supports this unique structure. As outlined in scheme (12), this compound can be derived only from the diradical (33b) suggesting that the cyclopentaindene product is also the structure derived from this diradical and that there is no participation of the benzocyclopropene (32) in the decomposition.

The gas phase pyrolysis of 1,2,3,3a-tetrahydro-7-fluoro-10-(p-fluorophenyl)benzo-[c]-cyclopenta-[f]-1,2-diazepine (5c) at 400°, was studied in collaboration with Mr. G.M. Baird,[96] and this supported the above conclusion. Again, thermal elimination of nitrogen occurred to give a product mixture showing a four peak glc trace (2½% OV1, 200°). GLC-mass spectrometry showed that each peak was due to one of the isomeric hydrocarbons of molecular weight 268. The mixture was hydrogenated, and, as before, this resulted in a simpler mixture of only two hydrocarbon/...

hydrocarbon products of molecular weight 270. An attempt was made to separate these as in the previous two cases, but here, only an incomplete separation was obtained. One compound, (35c), was obtained in a pure state (11%) although the overall yield of hydrogenated product was 83%. However, the nmr spectra of the pure compound and the mixture showed quite clearly that reaction had taken place in the same manner as before. The pure compound showed an aromatic multiplet at 2.9τ integrating for seven protons; a doublet at 5.4τ (J = 8 cps), a multiplet at 6.4τ and a quintuplet at 6.95τ (J = 8 cps), all integrating for one proton. The latter three resonances correspond to the three methine protons of structure (35c). Finally, there was a complex aliphatic multiplet between 7.5τ and 9.2τ corresponding to the six methylene protons. The mixture showed a complex aromatic region, the three methine resonances mentioned above and the same type of complex aliphatic region. Besides these however, there was an additional resonance at 6.04τ (doublet, J = 8 cps) which is consistent with the 9-fluorenyl proton of structure (37c). Again, these characteristic groups of lines were sharp, indicating that only the one set of products was present, and that these were derived from the diradical (33c), by analogy with the decomposition of (5b).

The/...



Scheme (10)

The general conclusion is then, that, at 400° in the gas phase, the benzodiazepines (5a), (5b) and (5c) thermally eliminate nitrogen to form mixtures of alkenes by a diradical route which may be described by scheme (10), (for (5a)), and that there is no participation of a benzocyclopropene in the decomposition. Furthermore, by analogy with the decomposition of acyclic azo-compounds,* formation of the diradical is probably via a one-bond scission mechanism in which the aliphatic C-N bond is broken first to form the more stable nitrogen-containing diradical (24) as shown in scheme (7a). Rupture of the second C-N bond probably follows rapidly to give the nitrogen-free diradical (25) which goes on to give the products by schemes (8) and (9). The absence of a benzocyclopropene is presumably due to the fact that the chemistry of these compounds is dominated by reactions involving thermal cleavage of the three-membered ring,[101] and conditions in the pyrolysis furnace are too vigorous for this ring system even to be formed, so that reaction proceeds by way of diradical species.

III Thermolysis of 3H-1,2-Benzodiazepines in Organic Solvents

The thermolysis of the benzodiazepines (5a) and (5b) has been/...

* See Introduction

been studied in various solvents at temperatures between 110° and 216°, and (5c) has been thermolysed in xylene (133°). Reaction times for complete decomposition varied between 45 minutes (dodecane, 216°) and two weeks (toluene 111°). 1,2,3,3a-Tetrahydro-10-phenylbenzo-[c]-cyclopenta-[f]-1,2-diazepine, (5a), on complete reaction, gave a mixture of several isomeric products of molecular weight 232 as shown by glc and glc-coupled to mass spectrometry (1% SE30, 170°). In some solvents, the product contained some 10-20% of solvent dimers (of the bibenzyl type, for example) and/or polymeric material. For example, thermolysis of 5a in xylene gave only a 50% yield of volatile product (assuming product molecular weight of 232) and about ten times as much polymeric material (by weight), while the corresponding reaction in chlorobenzene (ca. same temperature), gave a 90% yield of volatile product and only about 10% of high molecular weight material. Product yields were obtained by glc. When this work was first carried out, satisfactory methods for the independent preparation of the products had not been developed, so a true calibration for the internal standard technique could not be obtained. Instead, the assumption was made that since the products were so similar, being of molecular formula $C_{18}H_{18}$ or $C_{18}H_{20}$, they should have very similar responses to the gc detector. Given the same/...

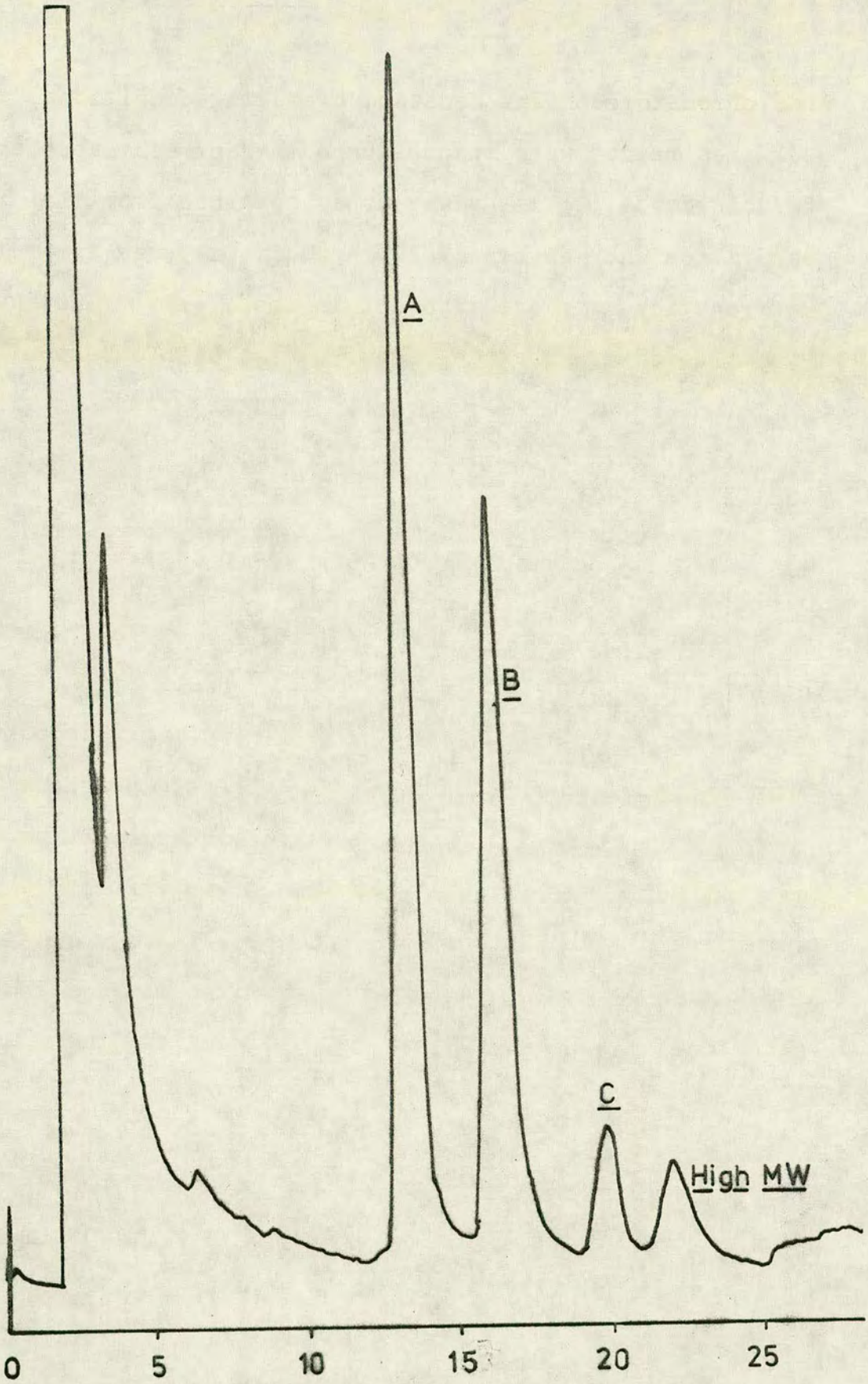
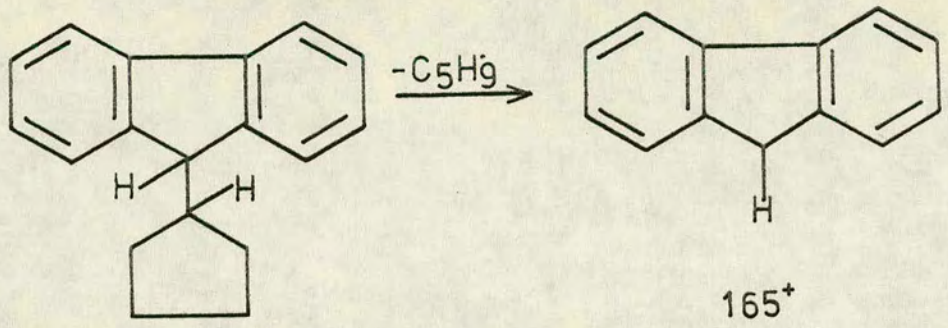


Fig. (xi)

same chromatograph and constant operating conditions, peak area ratios were then assumed to represent absolute product ratios. Yields were then obtained from the peak ratios and weights of the product mixtures after hydrogenation, and are recorded in table (1). This type of detector-response behaviour has been observed (see ref. 125) for the gas liquid chromatography of like compounds when the carrier gas was helium.

Two major products, A and B, were observed along with a third minor product C in the higher temperature reactions. Products B and C were shown, by their glc retention times (1% SE30 170°, 2% NPGS 190°, 2½% OV1 200°) to be compounds (8) and (9) respectively (fig. (xi)). These assignments were confirmed by glc/ms. Product A had the shortest glc retention time and a molecular ion of m/e 236. Thus, the compound giving rise to A must contain two double bonds. The first fragmentation in the mass spectrum of A was to 167^{+} (the base peak), which is very similar to the corresponding fragmentation in (9):

a)

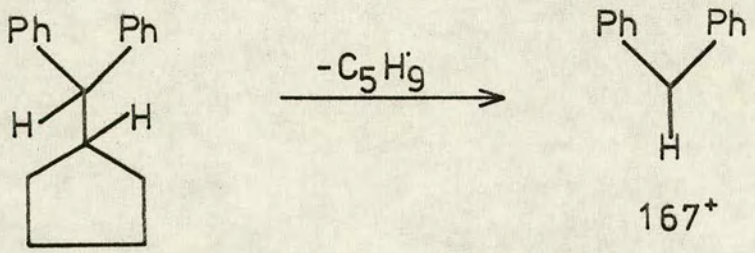


$234^{+\cdot}$

(9)

165^{+}

b)

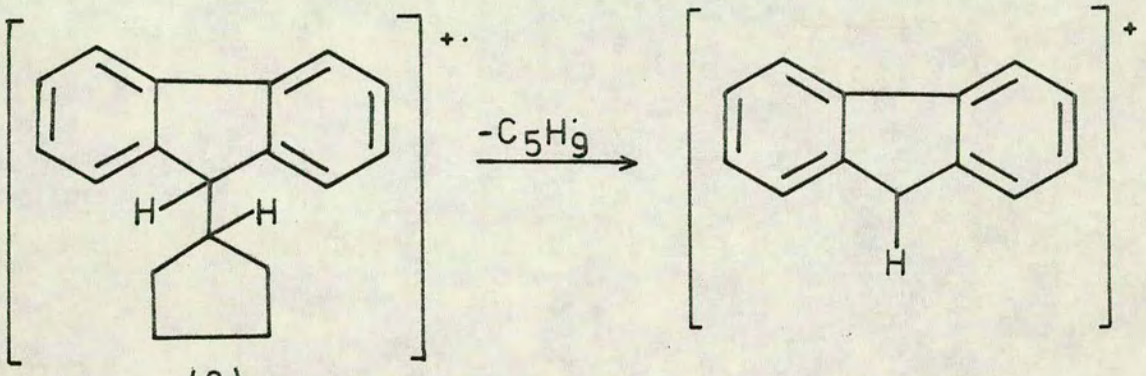


$236^{+\cdot}$

(38)

167^{+}

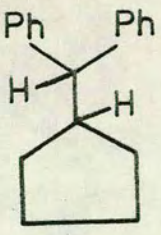
Scheme (13)



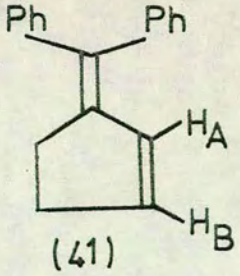
(9)

$234^{+\cdot}$ 165^{+} (base peak)

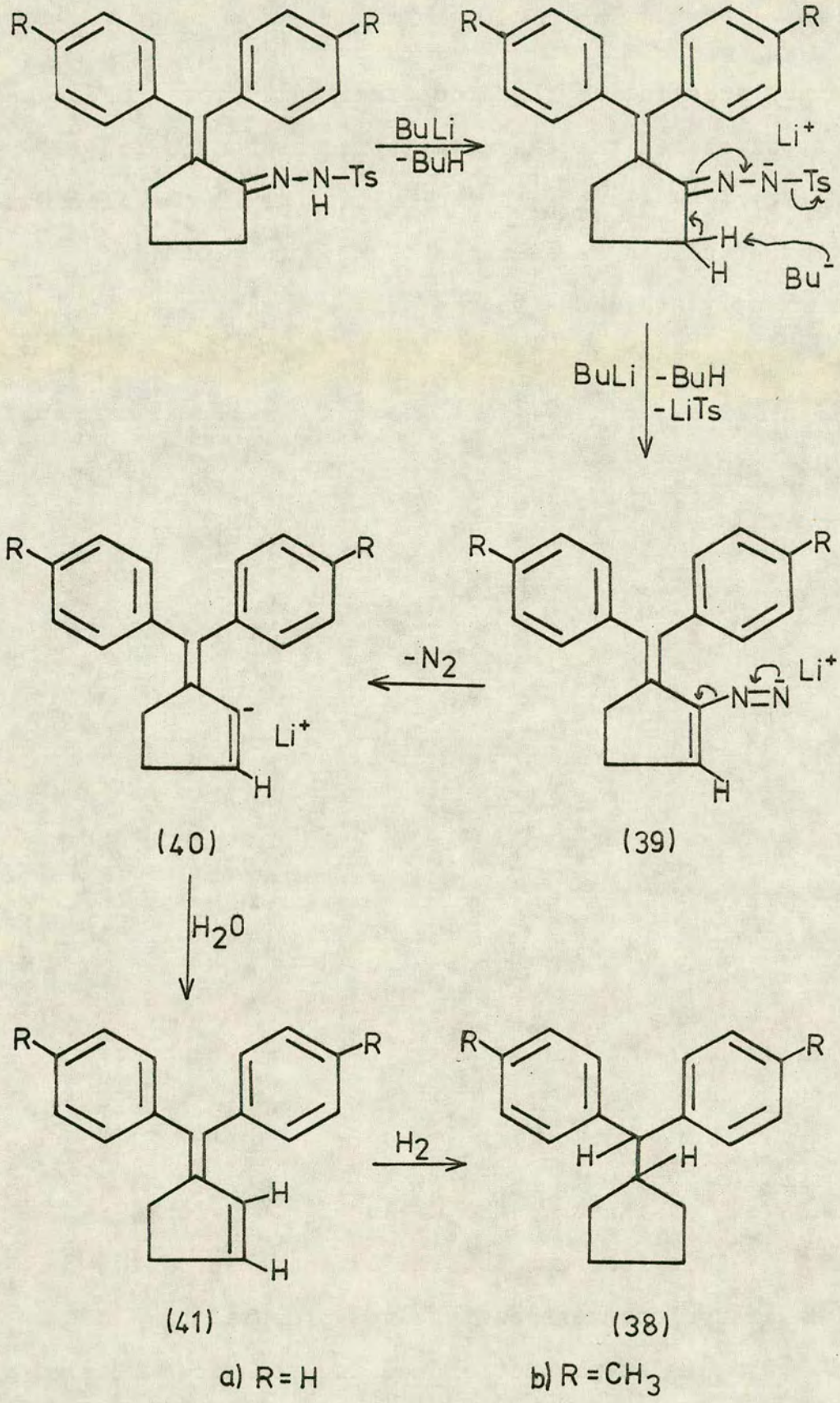
On this basis, the tentative assignment of structure (38) was made for A, and (41) for its pre-hydrogenation precursor:



(38)



(41)



(40) (39)

(41) (38)

a) R = H b) R = CH_3

Scheme (14)

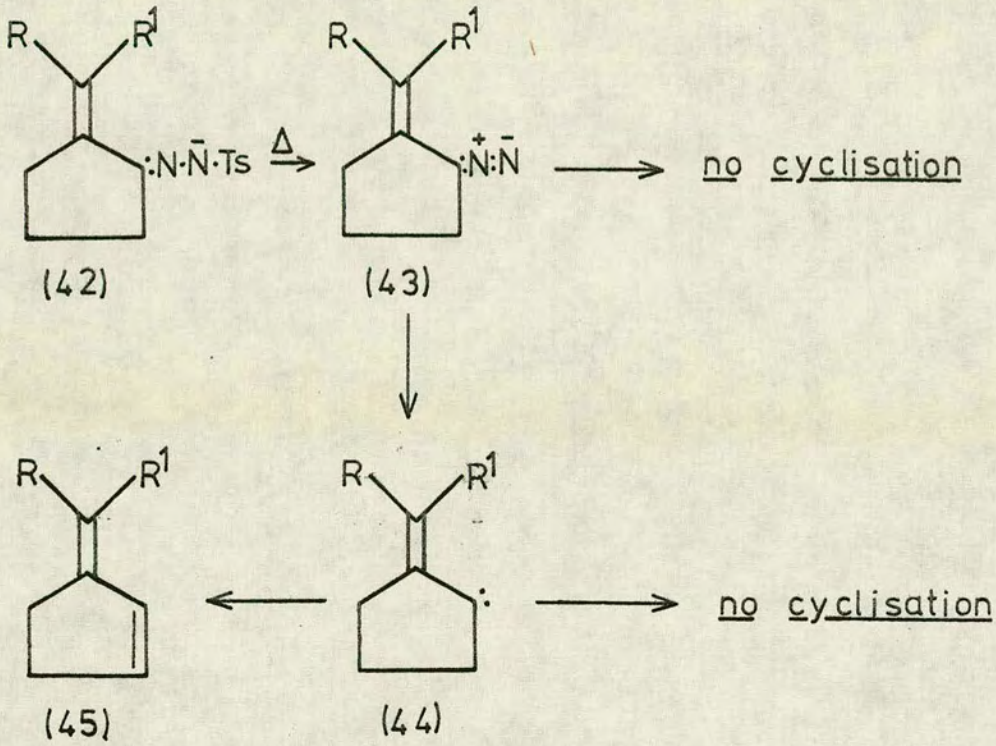
The nmr spectrum of the product mixture from the dodecane reaction showed the characteristic resonances of (19) and (12)/(14) along with two multiplets in the olefinic region which can be assigned to H_A and H_B of (41). These are exactly analogous to the corresponding protons in some 3-methylenecyclopentene derivatives which have already been prepared by Thorogood.[25] The assignments were proved by independent syntheses of (38) and (41). The latter was prepared by the method of Shapiro and Heath[7] (see Introduction p. 4) which was to react the toluene-p-sulphonylhydrazone of 2-diphenylmethylene-cyclopentanone with an excess of strong base at room temperature. This resulted in decomposition of the tosylhydrazone via the anions (39) and (40) to afford 3-diphenylmethylenecyclopentene (41), complete hydrogenation of which gave diphenylmethylcyclopentane, (38) (scheme 14). The nmr spectrum of (41) consisted of an aromatic multiplet at 2.84τ (10H), two low field olefinic multiplets at 3.64τ (1H) and 3.88τ (1H) which were assigned to H_A and H_B respectively, and two closely-spaced aliphatic multiplets at 7.28τ (2H) and 7.46τ (2H) which were assigned to the C_4 and C_5 methylenes respectively. This spectrum is similar to those of the 3-methylenecyclopentene derivatives prepared by Thorogood.[25] The hydrogenated product showed an aromatic multiplet at 2.8τ (10H), doublet at 6.5τ (J = 11 cps 1H), multiplet at 7.36τ (1H) and complex multiplet between 8.2τ and 9.0τ(8H). These/...

Product Yields for the Solution Phase Decomposition of (5a)

Solvent	bp	Yield of pyrolysis pdct.	Yield of high M.W.	D_1 recovered	Yield of hydrogenation Product A	B	C	Total
Dodecane	216°	85%	15%	-	38%	31%	10%	79%
Mesitylene*	165°	80%	20%	-	13%	54%	8%	75%
t-Butylbenzene	160°	80%	20%	-	22%	38%	2%	62%
Xylene*	135°	50%	much polymer	-	8%	36%	2%	46%
Chlorobenzene	132°	90%	10%	-	36%	42%	-	78%
Toluene*	111°	90%	10%	-	26%	59%	-	85%
Benzene!	78°	10%	13%	77%	Satisfactory analysis not obtained			?
Gas Phase	400°	90%	-	-	1%	34%	46%	81%

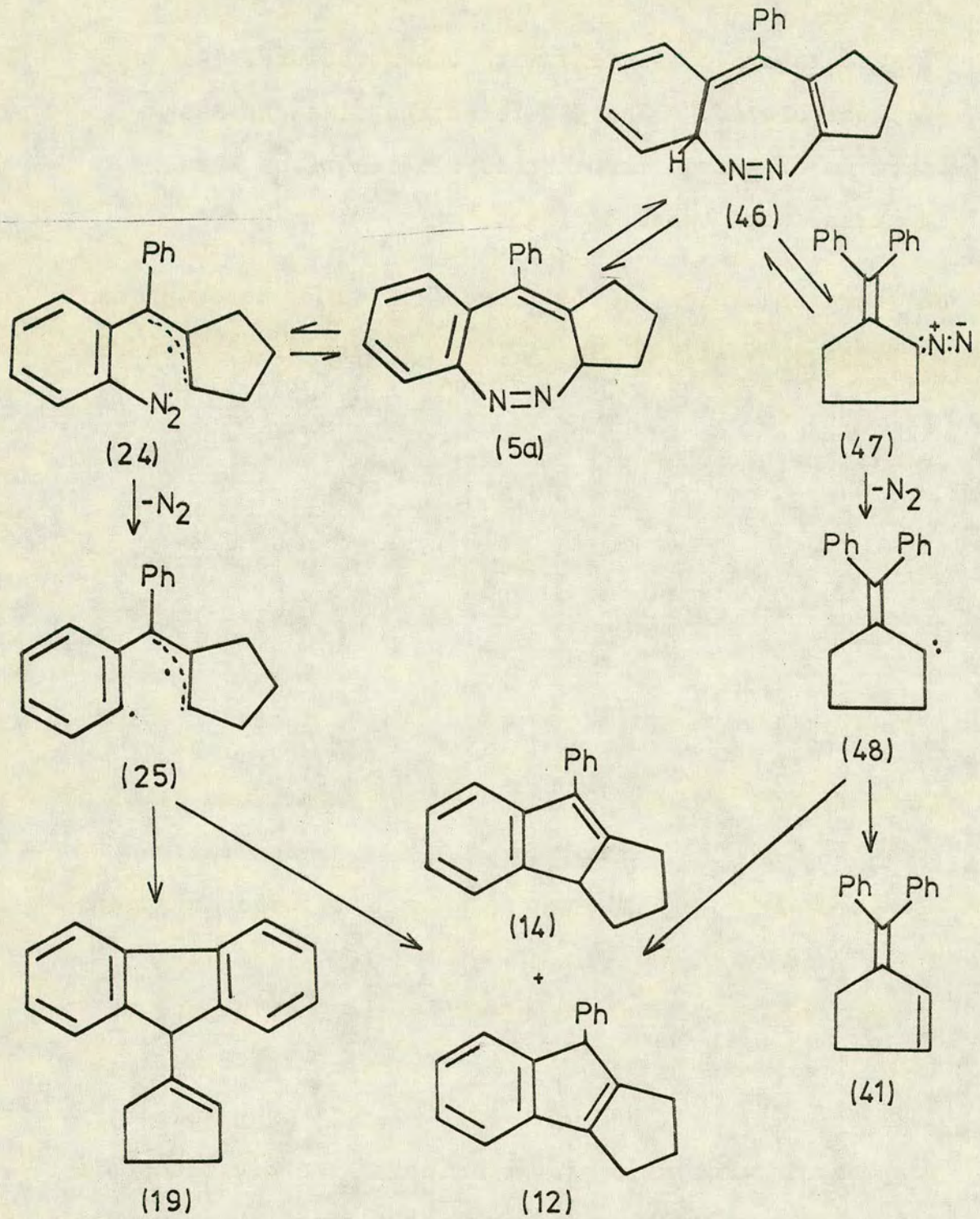
TABLE (1)

* Some bibenzyl-type product observed ! 77% diazepine recovered



R, R^1 = Alkyl

Scheme (15)


Ph
H
N=N
(46)
Ph
N2
(24)
Ph
N=N
(5a)
Ph Ph
(47)
-N2
Ph
(25)
Ph Ph
(48)
Ph
(14)
+
Ph
(12)
Ph Ph
(41)
(19)

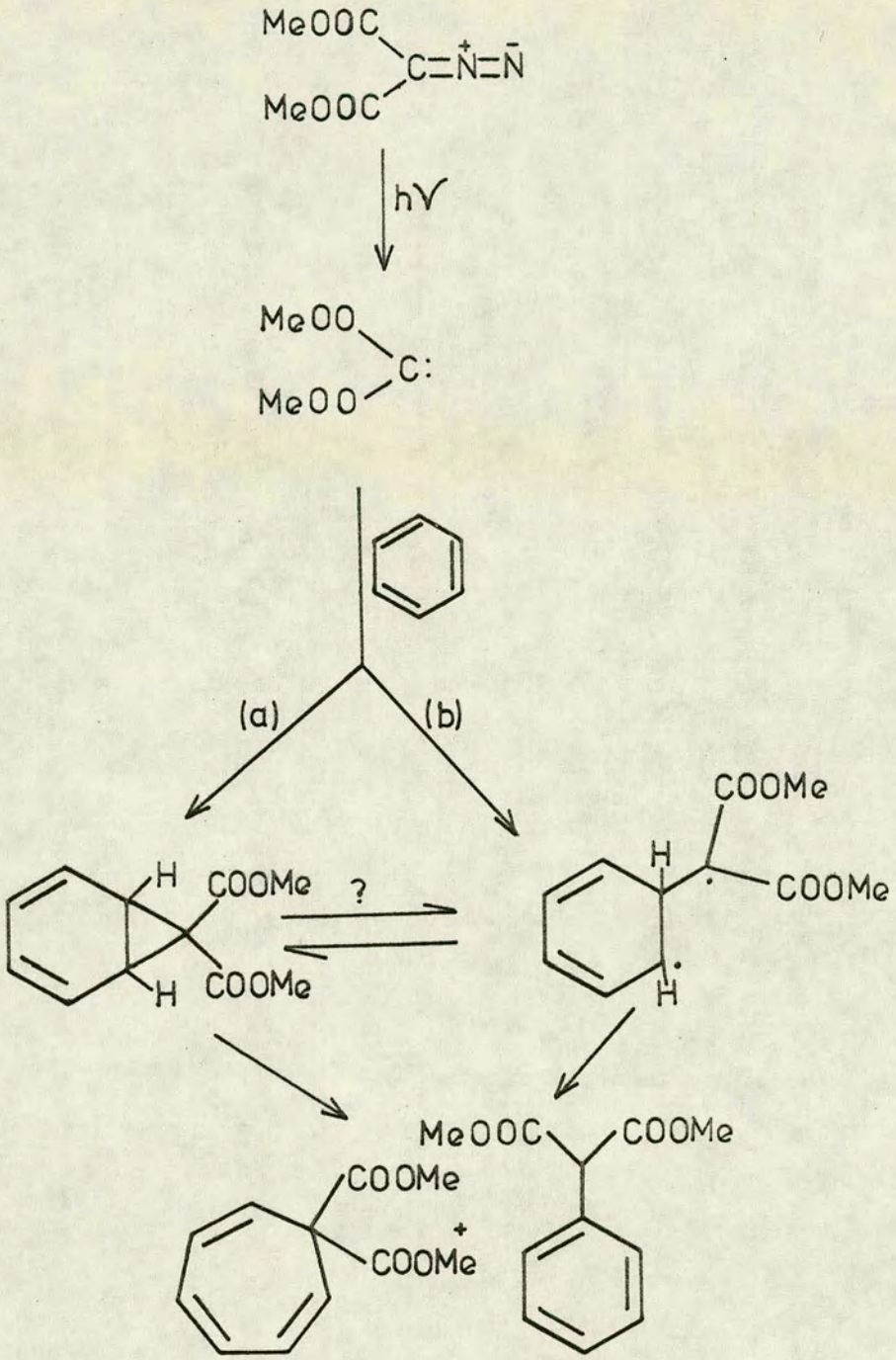
Scheme (16)

These data are consistent with the structures (41) and (38) postulated. The glc retention time and mass spectrum of A from the thermolysis reactions were identical with those of (38).

As shown in table (1) the diene (41) was a major product of the decomposition along with (12) and/or (14) whereas (19) was formed only in low yield, and only in the higher temperature reactions. The formation of (41), and low conversion to (19) are not readily interpreted on the basis of the diradical mechanism discussed previously (schemes (8), (9) and (10)). It is suggested therefore that a second mechanism is operating in competition with the diradical route at the lower temperatures in solution.

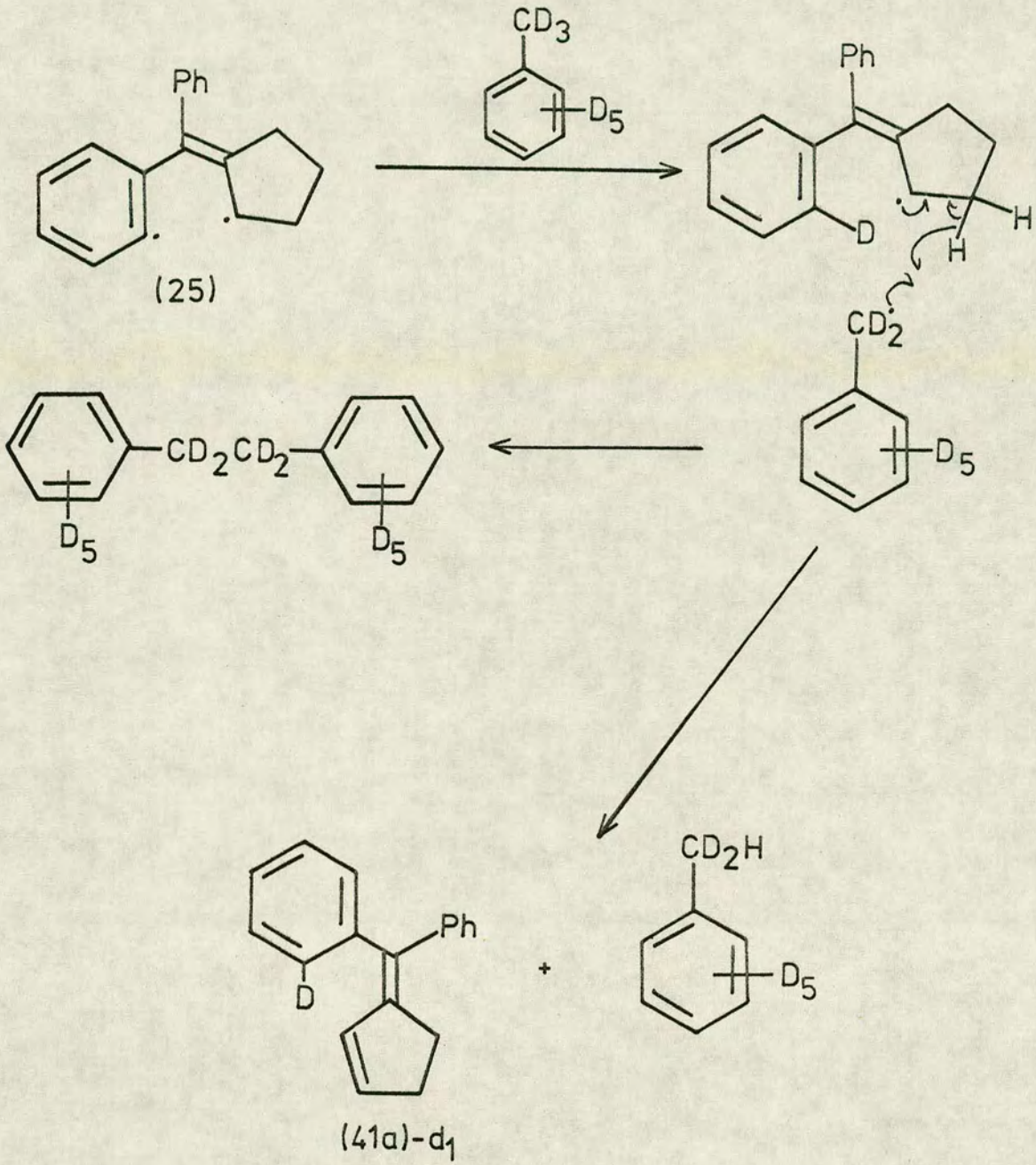
It is known* that thermolysis of tosylhydrazone salts of type (42) results in the dienes (45) via the diazo-compounds (43) and carbenes (44) as indicated in scheme (15). It is probable therefore that (41) is also formed from a carbene precursor in the thermolysis of (5a). A possible mechanism is outlined in scheme (16). The key steps are the 1,5-hydrogen shift to give (46) and the electrocyclic ring opening to the diazocompound (47) which reacts by nitrogen loss to form the carbene (48). A 1,2-hydride shift then gives rise to the diene (41), a reaction for which there is ample precedent.[11,12] Insertion of the carbene into the aromatic o-carbon-hydrogen/...

* See Introduction p.18

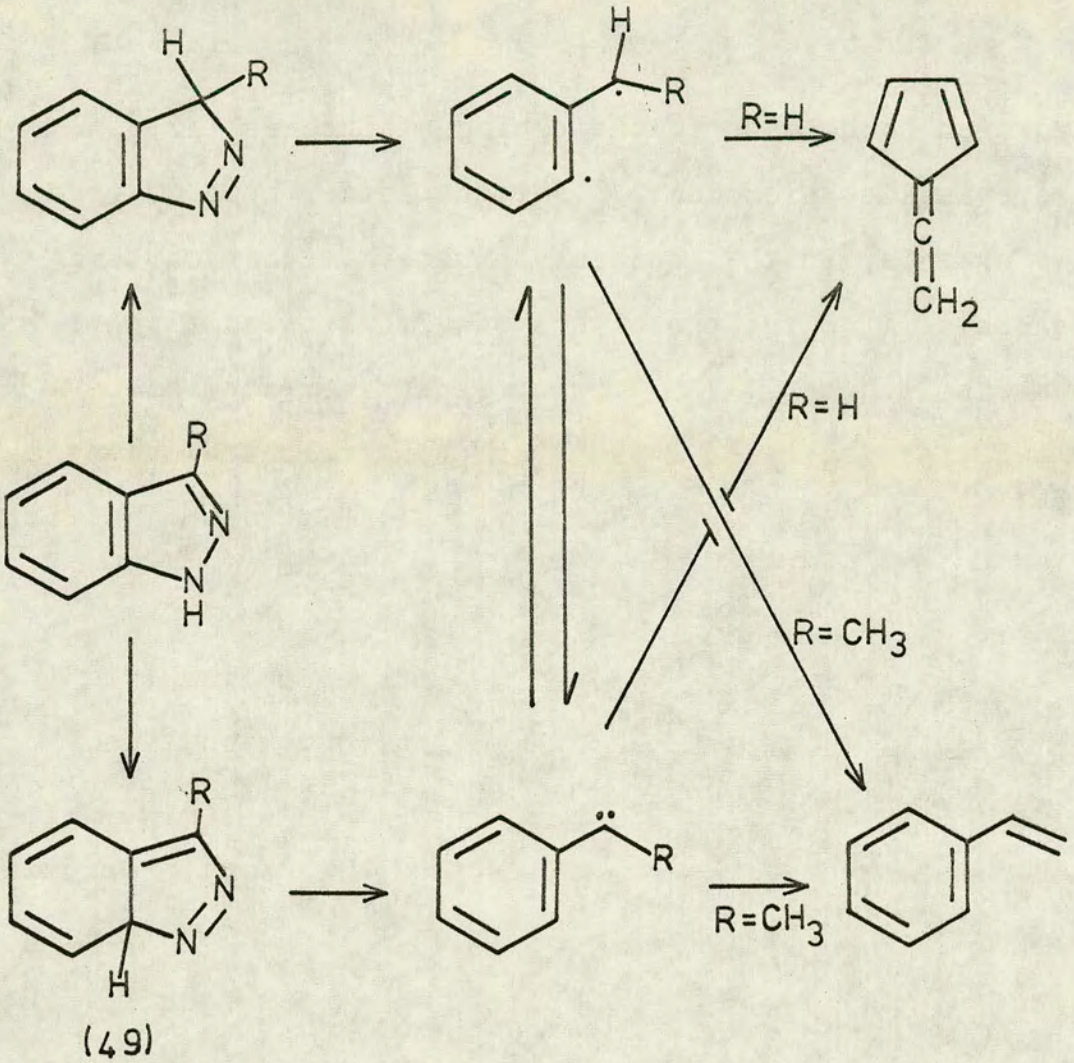


a)	2·7	:	1	(direct)
b)	1·6	:	1	(Ph_2CO-sensitised)

Scheme (17)



Scheme (18)



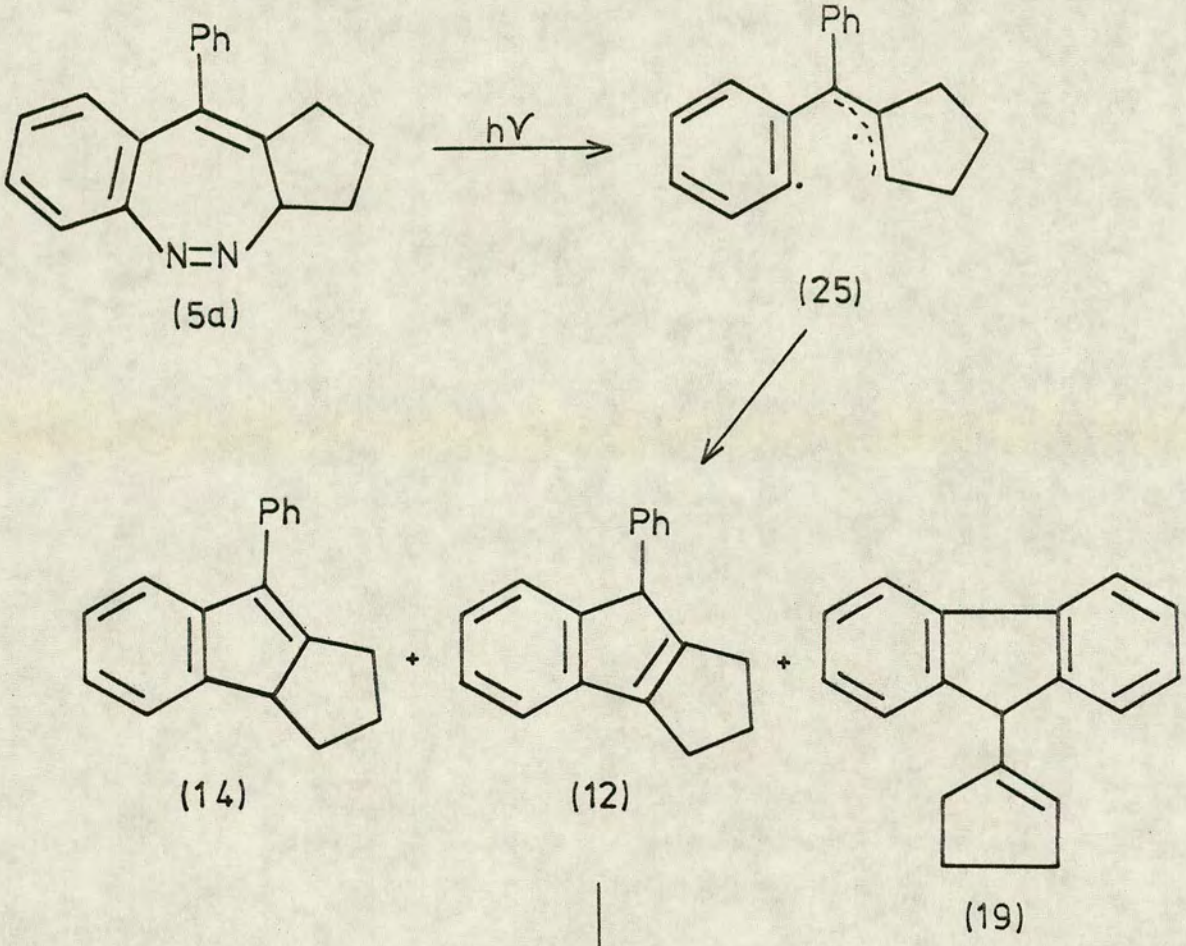
(49)

Scheme (19)

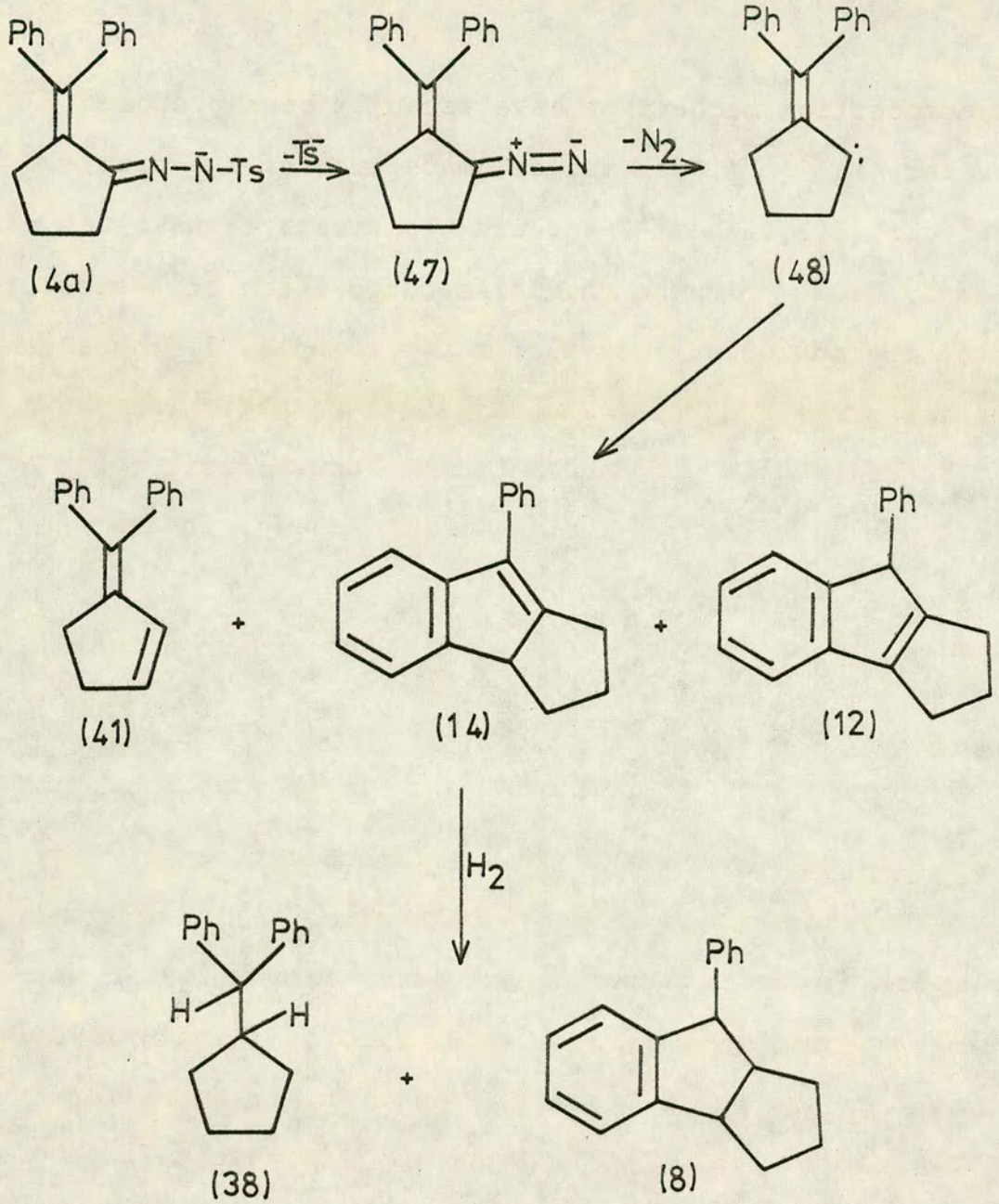
hydrogen bond leads to the cyclopentaindenes (12) and (14). There is also precedent[104] for the latter type of reaction, for example, in the addition of dicarbomethoxycarbene generated from the photolysis of methyl diazomalonate, to benzene (scheme 17). Triplet sensitiser studies have shown that increased amounts of phenylmalonate over the hexatriene product are consistent with increased participation of the diradical intermediate.

The possibility that (41) could be derived from the diradical (25) by an abstraction-disproportionation sequence with the solvent (scheme 18) was ruled out by decomposing (5a) in perdeuteriotoluene. Any interaction with solvent would result in a diene product containing one deuterium atom per molecule. The mass spectrum of the product would then show a higher preponderance of a peak at 233 than the "normal" diene. In fact, the (M+1) /M ratios for two identical reactions carried out in toluene and perdeuteriotoluene were identical showing that no deuterium was incorporated in the product, thus ruling out solvent interactions of the type shown in scheme (18). However, formation of the carbene or the diene by hydrogen transfer in (25) are possibilities which, although unlikely, cannot be excluded.

As the reaction temperature was raised, the proportion of the diradical-derived product (19) increased, which is in accord with the dual mechanism proposed. Double decomposition/...



Scheme (20)


Ph Ph
N–N̄–Ts
-Ts
Ph Ph
N⁺=N̄
-N2
Ph Ph
(4a)
(47)
(48)
Ph Ph
Ph
Ph
(41)
(14)
(12)
H2
Ph Ph
H H
Ph
(38)
(8)

Scheme (21)

decomposition mechanisms have recently been proposed by Bergman[69,70,72] in the decomposition of 2,3-diaza-bicyclo-[3,2,0]-hept-2-ene and its dimethyl analogue* and by Crow[105] in the thermal decomposition of 3-substituted 1H-indazoles. In the latter example, 1,5-hydrogen shifts precede carbene and diradical-formation as shown in scheme (19). Formation of the intermediate (49), here, is analogous to the formation of (46) in the decomposition of (5a).

The suggestion that (41) and (19) are formed from different intermediates, (48) and (25) respectively, and that (12)/(14) are formed from both is supported by results from the photolysis of the benzodiazepine (5a). After hydrogenation, the products were (8) and (9) only suggesting the intermediacy of (25) (scheme 20). However generation of (48) by photolysis of the tosylhydrazone salt (4a) gave a product which on hydrogenation contained (38) and (8), but not (9), (scheme 21).

1,2,3,3a-Tetrahydro-7-methyl-10-(p-tolyl)benzo-[c]-cyclopenta-[f]-1,2-diazepine was also thermolysed in solution, giving rise to mixtures of alkene isomers of molecular weight 260. Hydrogenation afforded three products D, E and F, their yields being recorded in table (2) for reactions/...

* See Introduction pp. 35-37

Product Yields for the Solution Phase Decomposition of (5b)

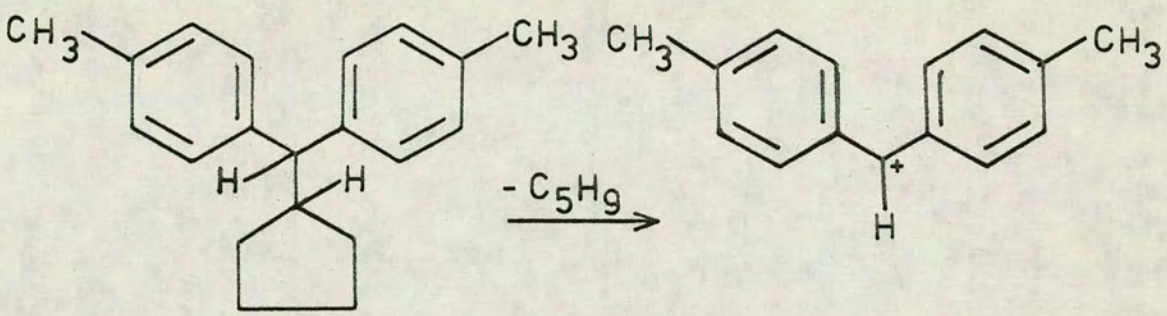
Solvent	bp	Yield of pyrolysis pdct.	Yield of high M.W.	Me-D_1 recovered	D	E	F	Total
Dodecane	216°			-	86%	trace	trace	86%
t-Butylbenzene	160°			-	41%	40%	7%	88%
Xylene*	135°	55%	20%	-	50%	-	-	50%
PhCl	132°	98%	-	-	62.5%	31.5%	-	94%
Toluene*	111°	60%	40%	-	20%	30%	-	50%
Benzene!	78°	26%	13%	49%	25%	-	-	25%
Gas Phase	400°	quant.	-	-		34%	46%	80%

* Some bibenzyl-type product observed

! 49% diazepine recovered

TABLE (2)

reactions at temperatures between 78° and 216°. Products E and F were readily identified as (35) and (37) respectively by their glc retention times (1% SE30, 170°; 2% NPGS 190°, and 2½% OV1 200°) and their characteristic glc-mass spectra. Product D was tentatively identified by its mass-spectral cracking pattern and by analogy with the unsubstituted case. Product D had a molecular ion of 264 and a base peak of 195, with no peaks in between. This suggests the structure (38b).



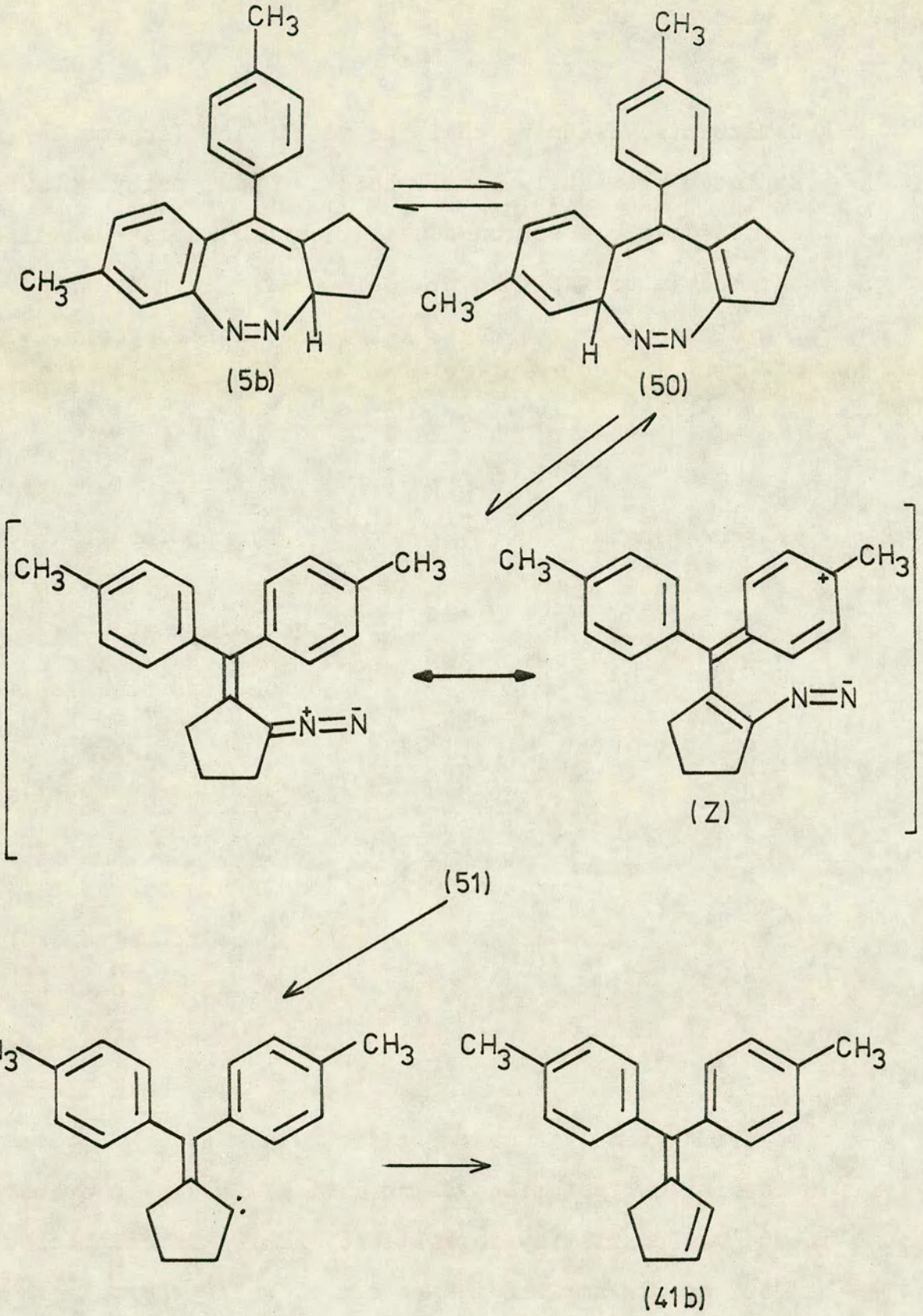
(38b)

$P^+ = 264$ base peak = 195

The authentic diene (41b) was prepared by the method of Shapiro and Heath[7] (scheme 14). Its nmr spectrum consisted of a firely split aromatic multiplet at 3τ (8H), olefinic multiplets at 3.7τ (1H) and 3.94τ(1H), an aliphatic/...

aliphatic multiplet between 7.20τand 7.60τ (4H) and a singlet at 7.70τ (6H). The olefinic multiplets are analogous to those previously observed[25] for 3-methylene-cyclopentene derivatives while the singlet at 7.70τ is characteristic of aromatic methyl protons. These data are consistent with the structure (41b) postulated. In the case of thermolysis in xylene, the only hydrocarbon product observed gave an nmr spectrum identical to that of (41b), confirming its identity. Hydrogenation of (41b) then gave (38b), identical to product D obtained from the thermolysis-hydrogenation sequence. The nmr spectrum of this compound is tabulated in Appendix I.7, and is consistent with the structure proposed. Identification of all three compounds was routinely achieved by their glc retention times and their characteristic glc-mass spectra.

By comparison of tables (1) and (2), it can readily be seen that corresponding reactions of the unsubstituted and dimethyl-substituted benzodiazepines correlate fairly well in terms of overall yield. However, the ratios of the products vary quite markedly in the two series of reactions, and in particular the proportion of diene product appears to be somewhat higher for the decomposition of (5b). The reason for this remains somewhat obscure, but must be connected with the two methyl substituents/...

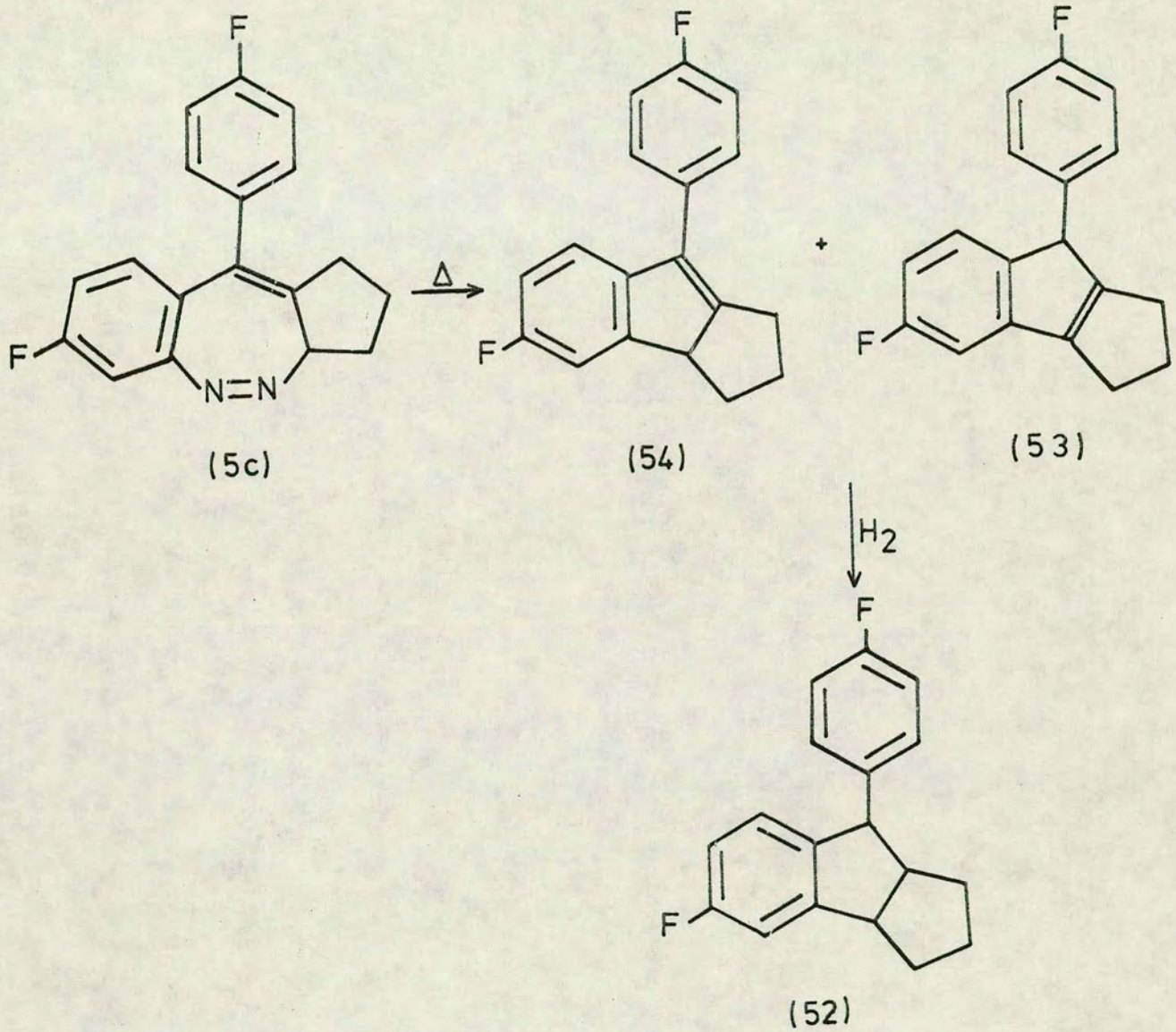


(41b)

Scheme (22)

substituents, assuming that the mechanism, (scheme 16), postulated previously, still holds. Now, methyl groups are inductively electron-donating, and electron-donating substituents destabilise diazoalkenes. Perhaps then, the two methyl groups destabilise the diazocompound (51) with respect to the carbene, e.g. by greater participation of forms such as Z (scheme 22), thus swinging the equilibria towards carbene-derived products. Perhaps also, the presence of the two methyl groups result in an easier conversion to the non-aromatic intermediate (50), and hence the carbene. However, this does not explain why all of the carbene results in diene product in solvents such as dodecane (216°), xylene (135°) and benzene (78°), to the complete exclusion of cyclopentaindene product. A study of the product-forming abilities of the carbene, generated from photolysis of the tosylhydrazone salt (4b) would have been informative here, but due to an oversight of the author, this experiment was not carried out.

1,2,3,3a-Tetrahydro-7-fluoro-10-(p-fluorophenyl)benzo-[c]-cyclopenta-[f]-1,2-diazepine (5c) has also been thermolysed in xylene, in collaboration with Mr. G.M. Baird.[96] In the initial reaction, Baird obtained a single product in 80% yield after hydrogenation. This was identified as (52) by its nmr and mass spectra. The thermolysis mixture consisted of two isomers in overall 95% yield, and these were shown by the characteristic resonances at 5.8τ and 6.45τ to be (53) and (54) respectively:



(5c) (54) (53)

(52)

The nmr spectrum of (52) was exactly analogous to those of (8) and (35) described previously. In two independent repeat reactions, <u>two</u> major products were observed after hydrogenation, in overall yield of 70%. These were shown by nmr glc/ms and argument by analogy with the decomposition of (5a), to be di-(p-fluorophenyl)methyl-cyclopentane/...

cyclopentane and (52) respectively. However, the ratios of the two reactions were not consistent, being 1:1.8 and 1:2.8. The inconsistency of these results is not understood at this time since the only difference in these reactions was the concentration of diazepine used which was twice as high in the first case. These are the only results available for this thermolysis, but they appear to parallel those of the other diazepine decompositions.

One fact remains to be explained viz. (5a) does not decompose appreciably at 150° in the solid phase nor at 200° in the gas phase whereas it decomposes fairly rapidly in xylene solution at 135°. This is presumably due to the vastly increased probability of collisions of sufficient energy to promote decomposition in solution as compared with the solid and gas phases.

To sum up then, it would appear that compounds of structure (5) undergo thermal elimination of nitrogen in solution by the dual mechanism outlined in scheme (16), the carbene route being the major path. It should be noted however that cyclopentaindene products e.g. (12) and (14) could in principle be formed from (25) in the solution phase reaction, the absence of (19) being explained by a higher $\Delta G^{\ddagger}$ for its formation compared to (12)/(14). This however, does not seem very likely in view of the photolysis of (5a) (see section (VI) below.

IV Low Temperature Gas Phase Pyrolysis of 1,2,3,3a-Tetrahydro-10-phenylbenzo-[c]-cyclopenta-[f]-1,2-diazepine

The mechanistic differences between gas phase pyrolysis at 400° and solution thermolysis of (5a) stimulated an investigation into its low temperature gas phase behaviour. The experimental set-up was identical to that used previously with the exception that the furnace was packed with glass wool rather than quartz tubes.

At a furnace temperature of 300°, careful examination of the nmr spectrum of the product mixture showed three compounds to be present. There were present low field aromatic multiplets at 2.00τ and 2.24τ along with the expected complex multiplet at 2.8τ. Finely split multiplets at 4.20τ, 4.4τ and 5.3τ were also observed along with complex multiplets at 7.6τ and 8.2τ. The integration suggested that the resonances at 2.00τ and 4.40τ belong to the same molecule, and likewise those at 4.2τ and 5.30τ. The latter lines were identical to those previously described for the olefinic and 9-fluorenyl protons of 9-cyclopent-1-enylfluorene (19), thus identifying this compound in the reaction mixture. The resonance at 2.24τ is due to the aromatic proton adjacent to the azo-linkage in the benzodiazepine (5a). High speed liquid chromatography (HSLC) showed the second product/...

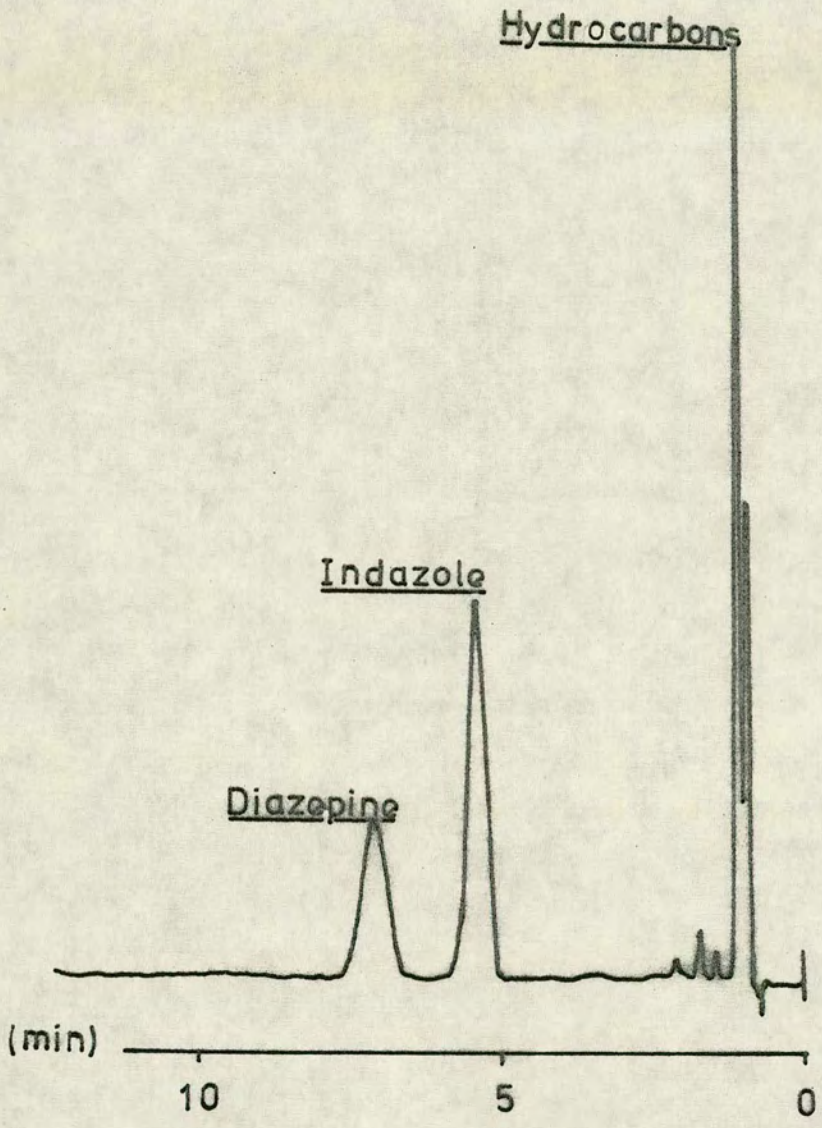
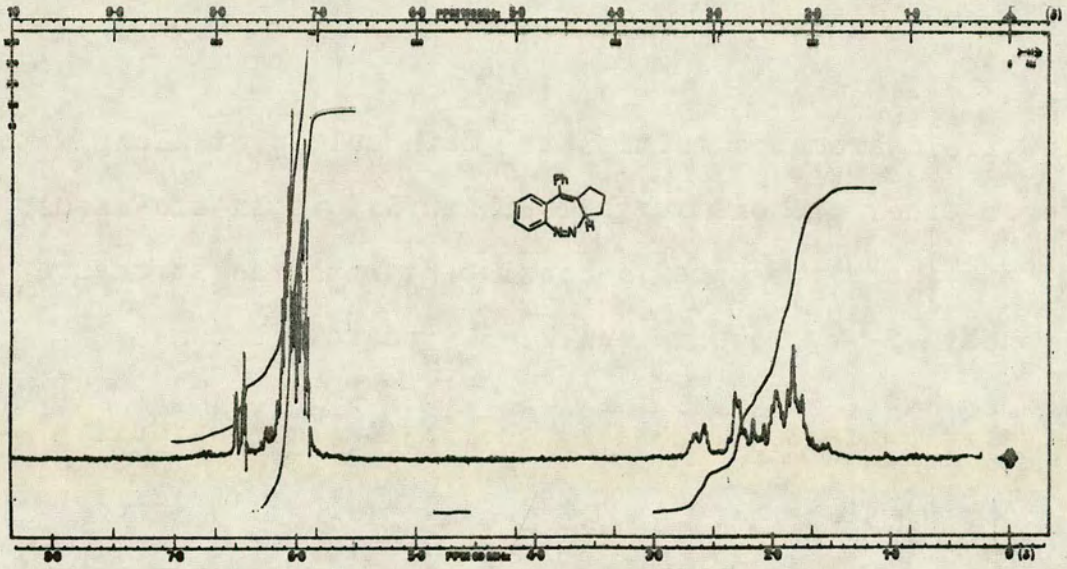


Fig. (xii)

product (55) to have a retention time intermediate between those of (19) and (5a) (fig. (xii)).

Lowering the furnace temperature to 280° led to an increased proportion of (55) relative to (19), but more unreacted diazepine was also present, as shown by the high speed liquid chromatogram. Subsequent reduction of the reaction temperature to 260° resulted in the formation of only one product along with unreacted diazepine in an approximately 1:1 ratio. These compounds were recognised by their characteristic nmr resonances (2.00τ, 4.40τ and 2.24τ, 6.84τ) and by HSLC to be (55) and (5a) respectively. Separation of the product was achieved by column chromatography on alumina using benzene as eluting solvent. The product (55) was eluted first. The combustion analysis of (55) was consistent with the formula $C_{18}H_{16}N_2$, but its mass spectrum showed a highest molecular weight peak of only 232, 28 less than the molecular weight of 260. This suggested a structure containing a very labile azo-group which could readily eliminate nitrogen thermally in the mass spectrometer probe. The nmr spectrum of (55) is shown in fig. (xiii) along with that of the benzodiazepine (5a). Compound (55) showed a low field aromatic multiplet at 2.00 (1H), aromatic multiplet at 2.8τ (8H), finely split olefinic multiplet at 4.44τ (1H), triplet at 7.7τ (4H) and quintet at 8.18τ (2H). The integration value of 1:8 for the

low/...



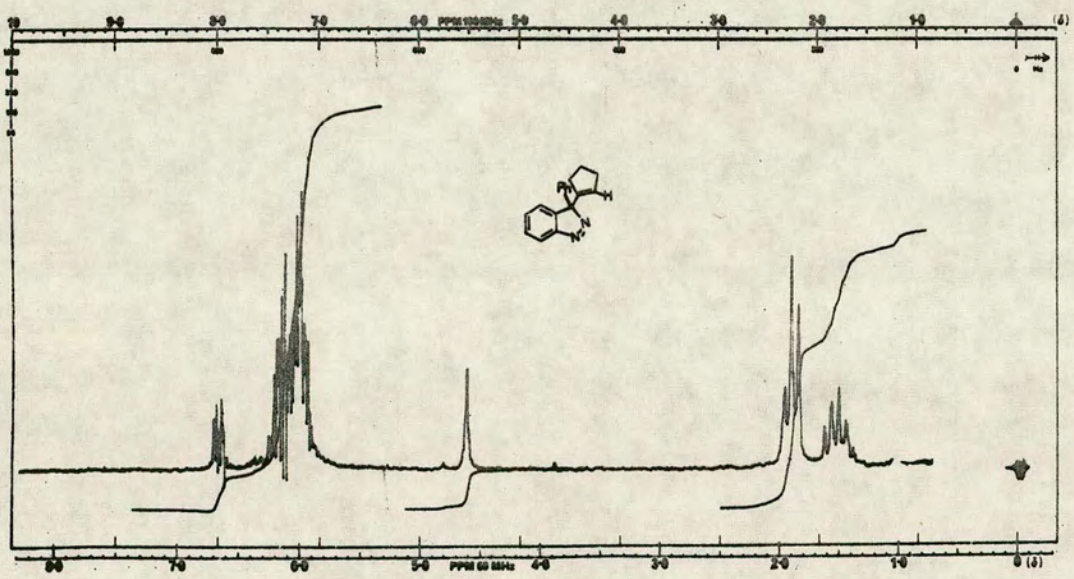


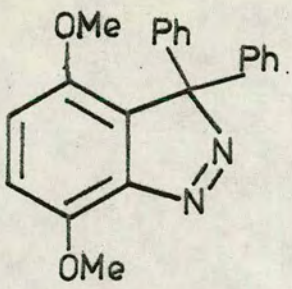
Fig. (xiii)

low field aromatic multiplet: main multiplet along with seven other protons suggests that (55) is an azo-isomer of (5a), and the data is consistent with the structure 3-phenyl-3-(cyclopent-1-enyl)-3H-indazole shown.

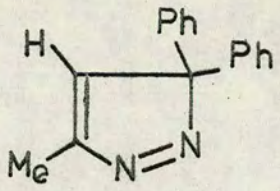
Further evidence supporting the 3H-indazole structure was obtained from its ^{13}C nmr spectrum and the differences between this and the ^{13}C spectrum of the benzodiazepine. The noise-decoupled spectra of the two compounds are very similar, consisting of eighteen lines each, one for each carbon atom. (Noise-decoupling effectively removes all carbon-hydrogen coupling so that each carbon atom gives rise to only one line thus simplifying the ^{13}C spectrum. This is achieved by applying a blanket of radio frequencies, covering the entire proton range, to the sample). The benzodiazepine spectrum showed four low-field lines, between 152 and 132 ppm from TMS, corresponding to four of the quaternary carbon atoms. Then follows a group of ten closely-spaced lines between 130 and 125 ppm from TMS. These fourteen lines correspond to the twelve aromatic and the two quaternary olefinic carbon atoms. Unambiguous assignments of these could not be made. Just above the deuteriochloroform triplet (internal lock) was a single line at 75ppm corresponding to the 3a-carbon atom. Downfield from TMS by 33, 32 and 27ppm were the remaining three lines corresponding

to/...

to C_1, C_3 and C_2 respectively. The spectrum of (55) was very similar in all respects except for the 3a-carbon atom. There was no resonance near deuteriochloroform, but instead, a new line at 100ppm from TMS thought to be due to C_3 of the indazole structure. This assignment was confirmed by comparison with the ^{13}C nmr spectra of (56) and (57), both of which[106,107] showed single lines near 100ppm from TMS due to the saturated ring-carbon atoms:

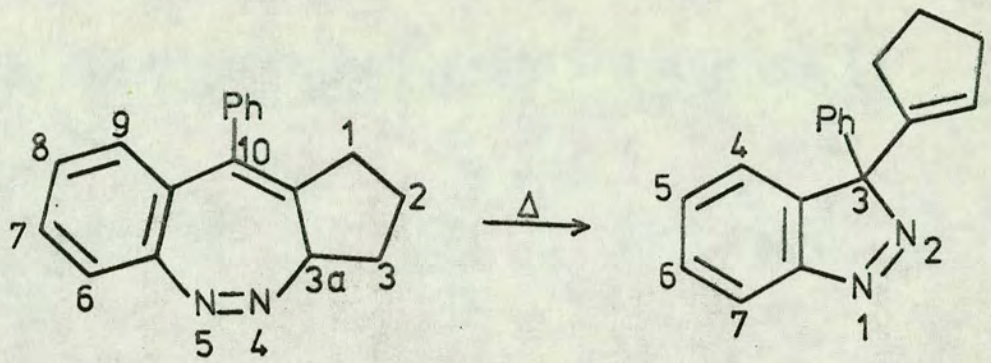


(56)



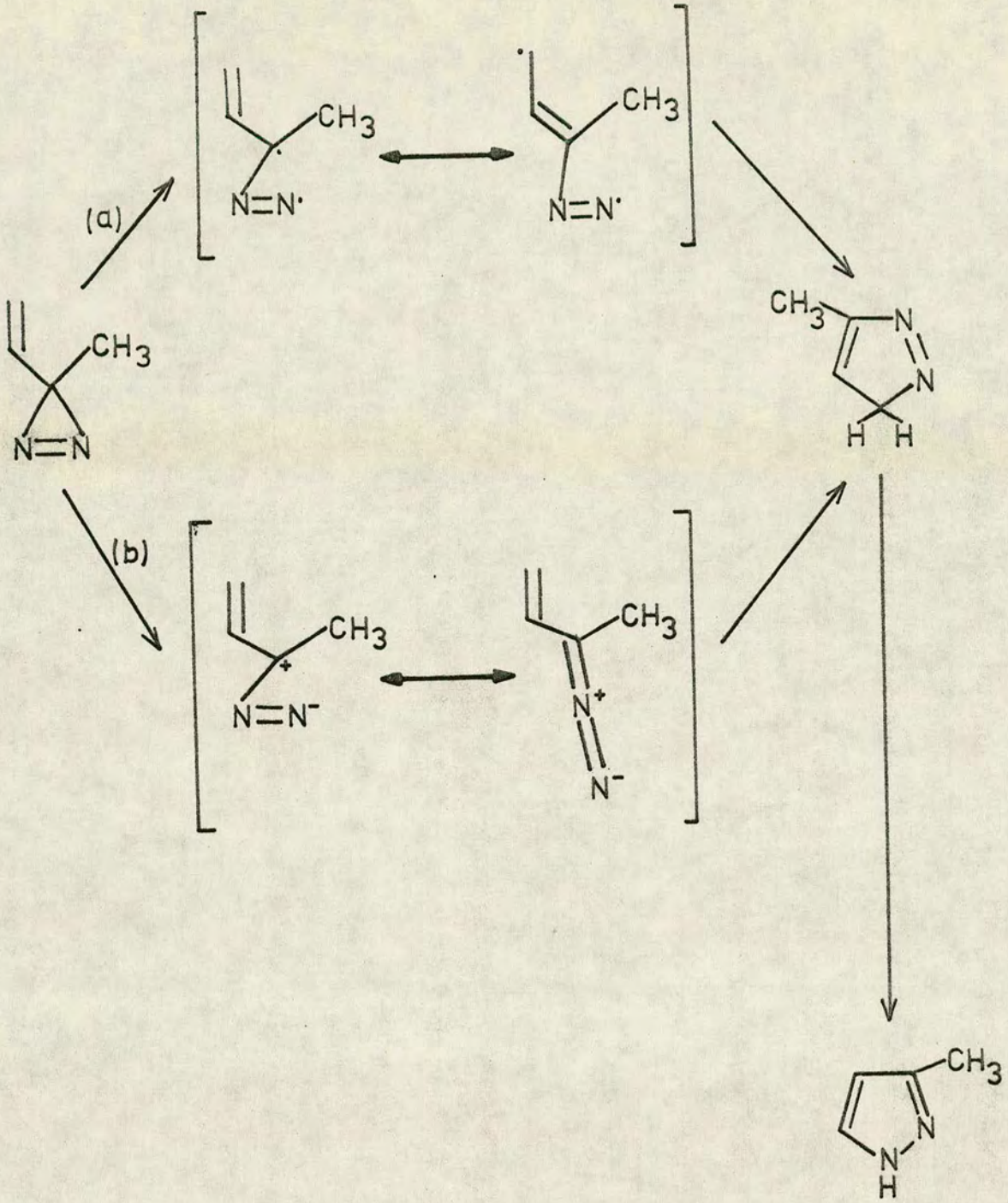
(57)

Thus, in reacting to the indazole, the benzodiazepine appears to have changed mainly at the 3a-carbon atom which is in agreement with the isomerisation suggested:

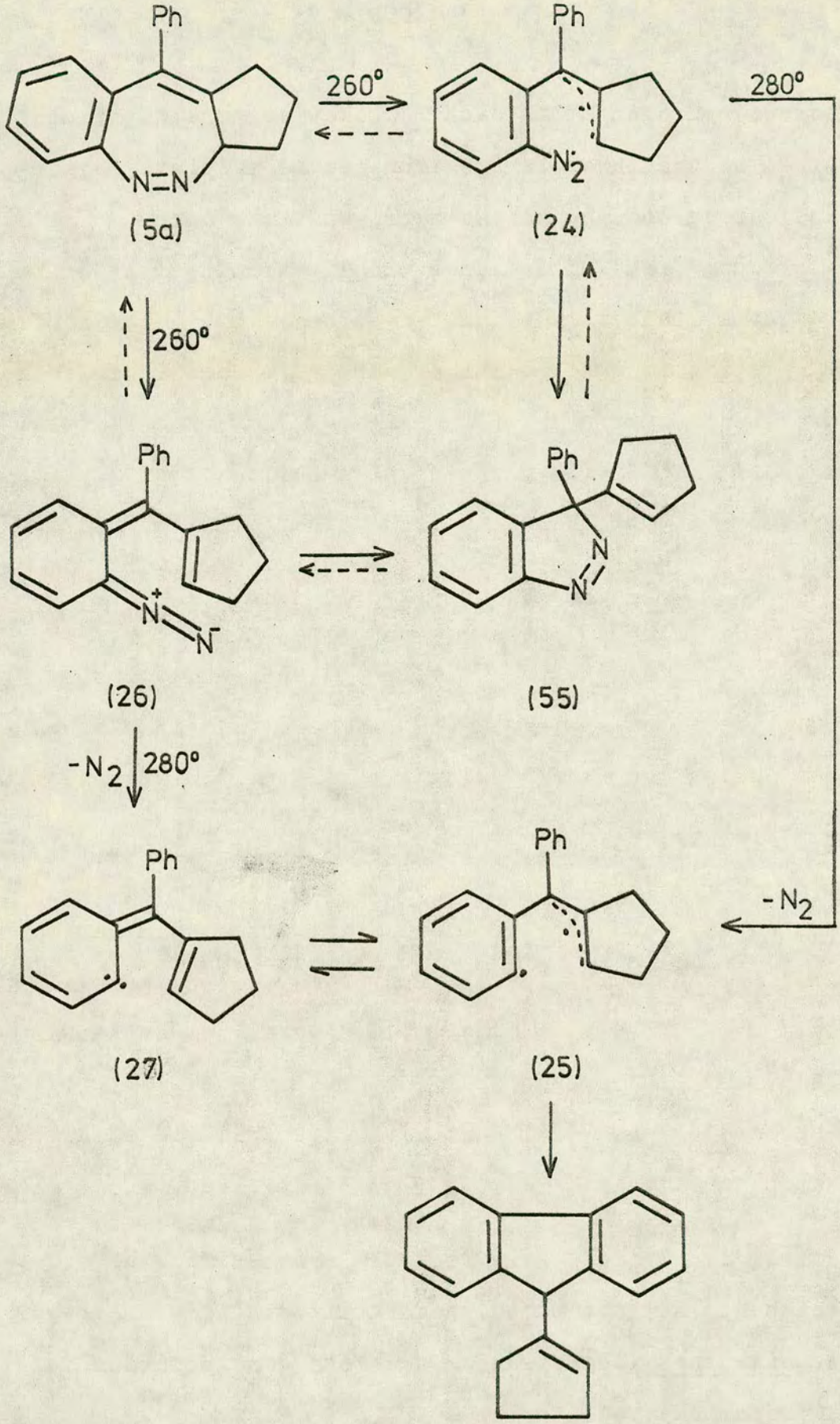


(5a) (55)

The off-resonance decoupled spectra confirmed these assignments. (Off-resonance decoupling has the effect of reducing the carbon-hydrogen coupling. The general procedure is to apply a large single radio frequency of a value which does not interfere with any of the sample resonances; usually, the TMS proton frequency is used. This results in reduction of the magnitude in the carbon-hydrogen coupling constants). The four low-field lines of the diazepine remained unsplit showing that these are due to quaternary carbon atoms. However, the line at 75ppm now became a doublet showing its coupling to only one hydrogen atom. The highfield lines all became triplets showing that they are bonded to/...



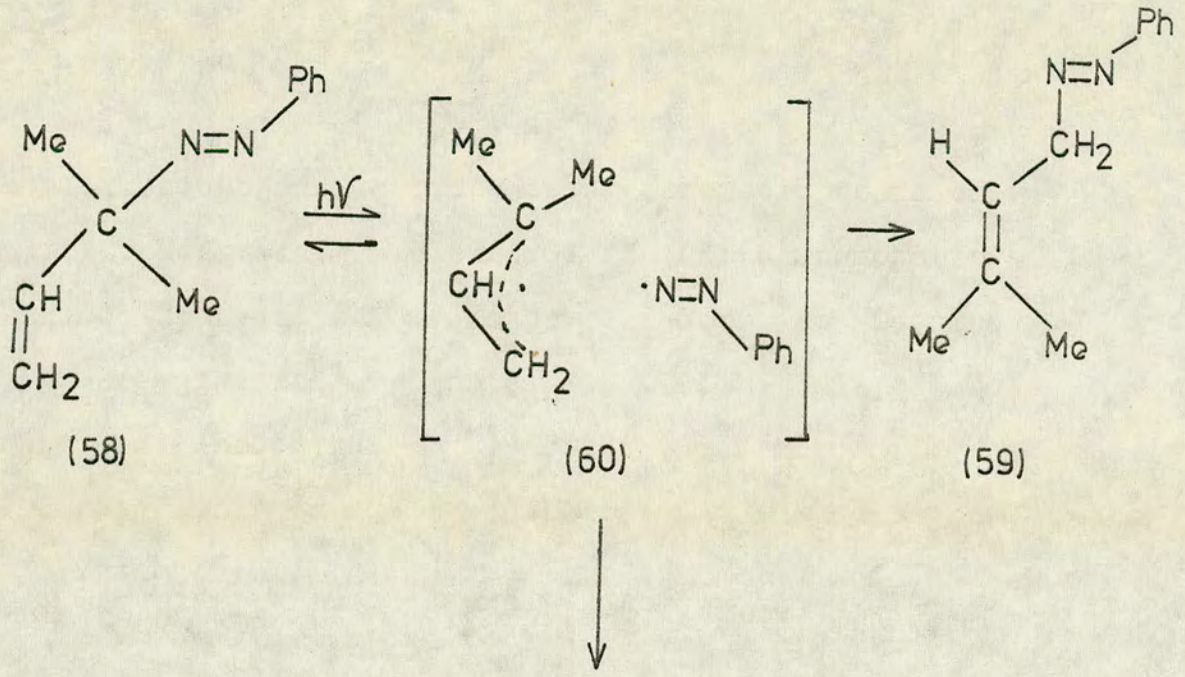
Scheme (23)


Ph
260°
Ph
280°
N=N
N2
(5a)
(24)
260°
Ph
Ph
N
N
N+
N-
(26)
(55)
-N2
280°
Ph
Ph
-N2
(27)
(25)
(19)

Scheme (24)

to two hydrogen atoms each. Likewise, the highfield lines in the indazole spectrum became triplets, again indicating bonding to two hydrogen atoms each. The line at 100ppm from TMS remained unsplit showing that it is due to a quaternary aliphatic carbon atom. The four lowfield resonances remained unchanged showing that these are also quaternary carbon atoms. Thus, the spectral and analytical data for the product obtained by pyrolysing (5a) at 260° in the gas phase, support its formulation as (55). The above isomerisation provides a unique example of the rearrangement of a seven-membered- to a five-membered- azocompound. The only comparable reaction is one, recently published by Liu and Toriyama,[108] concerning the ring-expansion of a 3-vinyldiazirine to the corresponding pyrazole (scheme 23). On the basis of kinetic evidence, they concluded that the mechanism involved was stepwise, but could not distinguish between diradical (a), and dipolar routes (b). On the basis of this work, it seems reasonable to postulate a similar stepwise mechanism for the isomerisation of (5a) to (55), (scheme 24), but it is similarly not possible to decide which intermediate (24) or (26) is involved.

Porter and Iloff[47] have recently synthesised the azocompound (58) and photolysed it in solution. As well as cis-trans isomerisation and some decomposition to hydrocarbon/...



Hydrocarbon Products

Scheme (25)

hydrocarbon products, these workers managed to isolate the new azocompound (59) in 20% yield. This isomerisation presumably occurred *via* the caged radical-pair (60) as shown in scheme (25). This observation suggests that (5a) might similarly react *via* the diradical intermediate (24) (scheme (26)), and some support for this possibility was obtained from the fact that in a reaction at 280°, some of the diradical-derived product (19) was also observed. Also, reaction *via* the diazocompound (26) would result in a loss of aromaticity in a benzene ring whereas this is not so in the case of reaction *via* the diradical (24). This again suggests that the latter may constitute the less energetic reaction path, and hence be preferred in the isomerisation of (5a) to (55).

V Re-examination of the Solution Phase Reactions

a) Preliminary Investigations

Since the solution phase thermolyses were initially studied with regard to complete decomposition of the benzodiazepines, these were now re-investigated as regards to possible indazole formation prior to decomposition. Formation of the indazole (55) in the gas phase reaction 260° raised several important mechanistic questions regarding the solution phase decompositions of (5a):

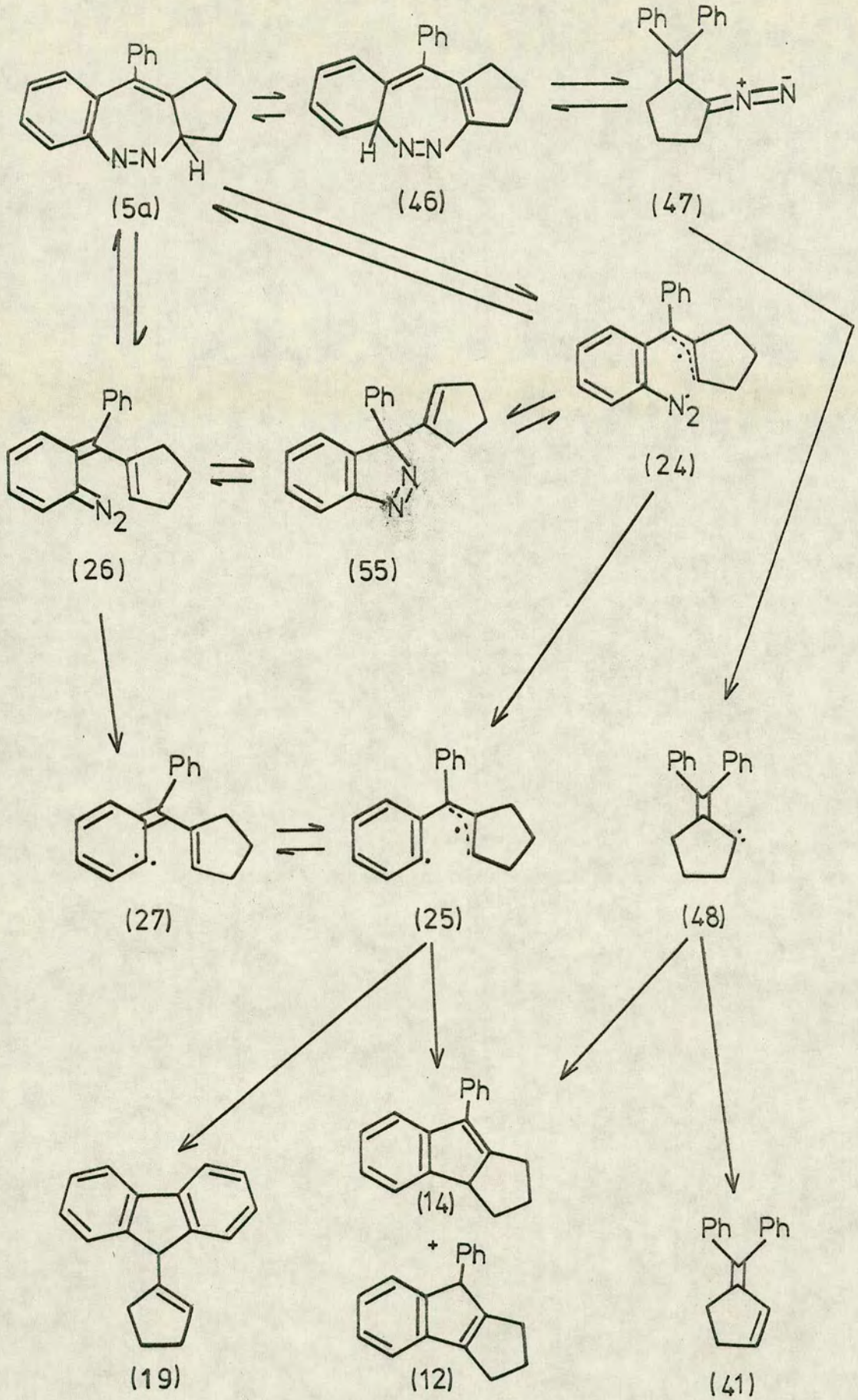
1) Was the indazole (55) formed in solution prior to the loss of nitrogen?

2) If (55) was present, was it in equilibrium with the benzodiazepine or was its formation an irreversible process?

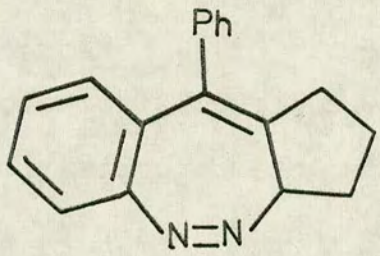
3) Were the hydrocarbon products formed from benzodiazepine or indazole, or both? If both, which products were derived from which azo compound?

In order to attempt to answer these questions, a technique for quantitative detection of both indazole and diazepine in the solution phase reactions had to be devised. The use of uv spectroscopy was ruled out because of the similar absorption envelopes for these two compounds, but nmr spectroscopy seemed an attractive alternative. The reactions were carried out in nmr tubes at various temperatures, and the tubes were periodically removed to the nmr instrument for examination. NMR peaks due to the indazole were observed at 135°, 165°, 178° but not at 212° when the decomposition was very fast (~ 20 min.). No CIDNP effects were observed for indazole or hydrocarbon product formation, but this does not provide conclusive evidence for the absence of radical intermediates as has been reported by Porter and coworkers.[50] A fifth reaction at 165° but starting with the indazole rather than the diazepine led to isomerisation to the diazepine.

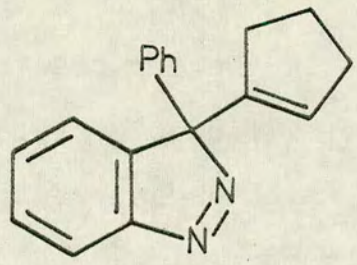
In/...



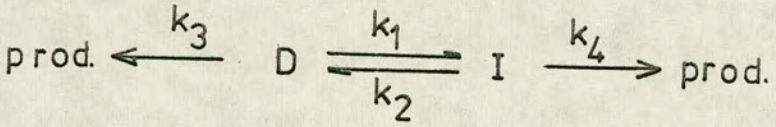
Scheme (26)

D = 

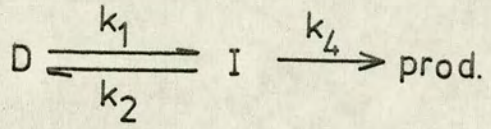
(5a)

I = 

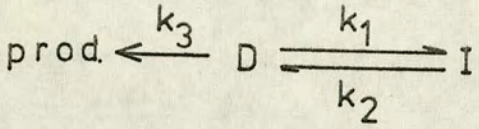
(55)



scheme A



scheme B



scheme C

Fig. (xiv)

In the two reactions at 165°, the peak area ratios (HSLC) of indazole:diazepine became identical after about 30 minutes and remained so to complete decomposition. The indication, then, is that the isomerisation is reversible and that (5a) and (55) interconvert at a faster rate then they decompose. This implies that the solution phase decomposition of (5a) is even more complex than suggested in scheme (16), and may be represented by scheme (26) in which the diazepine-indazole interconversion is shown as proceeding by a two-step process via either a di-radical or diazo-intermediate. However, it is also possible that this interconversion might be a concerted process proceeding via a "forbidden" concerted 1,3-sigma-tropic rearrangement[109] or by some process involving the nitrogen lone-pair orbital. Concerted sigmatropic migrations are generally characterised by a negative entropy of activation[110] while stepwise rearrangements are not.[108] It was therefore decided to attempt to investigate the kinetics of the diazepine-indazole inter-conversion and the following decomposition, and hence to differentiate between the three possible reaction schemes shown in fig. (xiv).

To carry out this kinetic investigation, it was necessary to find a more accurate monitoring technique than nmr, which, although it had effectively demonstrated the presence/...

presence of the indazole in the solution reactions, was not accurate enough for a quantitative kinetic investigation on this system. HSLC proved to be an ideal technique for this for several reasons:

1) detection of the compounds after separation was by a uv detector having a linear quantitative response;

2) operation was at room temperature, so cutting down the possibility of decomposition of the sensitive azocompounds during analysis.

3) speed of analysis was about ten minutes per sample.

As will become apparent, a complete kinetic analysis was not achieved, mainly because of the time element, but a suitable analytical technique was developed.

b) Application of High Speed Liquid Chromatography to Kinetic Analysis

i) General Technique and Comparison with GLC[111,112]

High Speed Liquid Chromatography (HSLC) is very similar to Gas Liquid Chromatography (GLC) in many ways, and in fact, Giddings[113,114] has shown that the theory developed for glc was equally applicable, with minor modifications, to liquid chromatography. Theory indicated that by using/...

using high pressures and very small particles, lc could rival glc both in speed and resolving power.[115]

Present equipment for HSLC[116] mirrors many of the features of glc, and present trends are towards systems with the same versatility, ease of spearation, cheapness and capacity for automation. Degassed solvent is pumped at a pressure of up to 3000 pound inch^{-2} through a column containing a finely-divided and well-graded partitioning material in the size range 10-50μm. Columns are about 2mm in diameter and 50 to 100cm long and flow rates are about 1ml min^{-1} so that unretained materials are eluted in about 1 min as in glc. Samples may be injected by an injection valve or microsyringe: a typical injection might be 1 to 10μl of a 1% mixture solution. Detection of the eluted compounds is usually by ultra-violet absorption photometers[117] which are very sensitive, but limited to substances which absorb at the particular wavelength used. (The limit of detection of a substance with a molar extinction coefficient of 10^4 is about 1 in 10^9).

HSLC has found important application in the analysis of drugs, pesticides, high molecular weight aromatic compounds, plasticisers, antibiotics, organic compounds generally and biochemicals. What follows appears to be the first attempted use of HSLC in kinetic analysis.

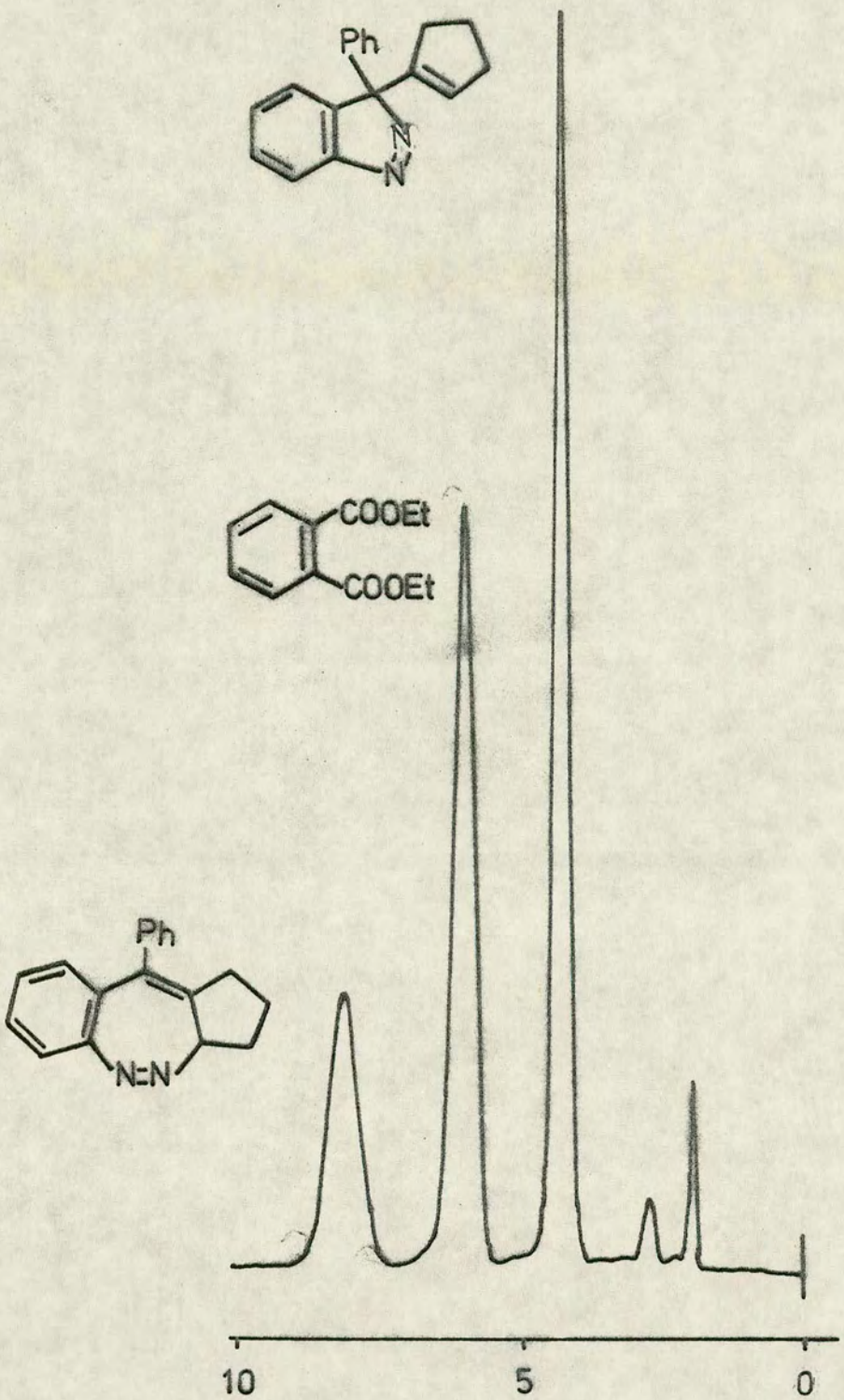


Fig. (xv)

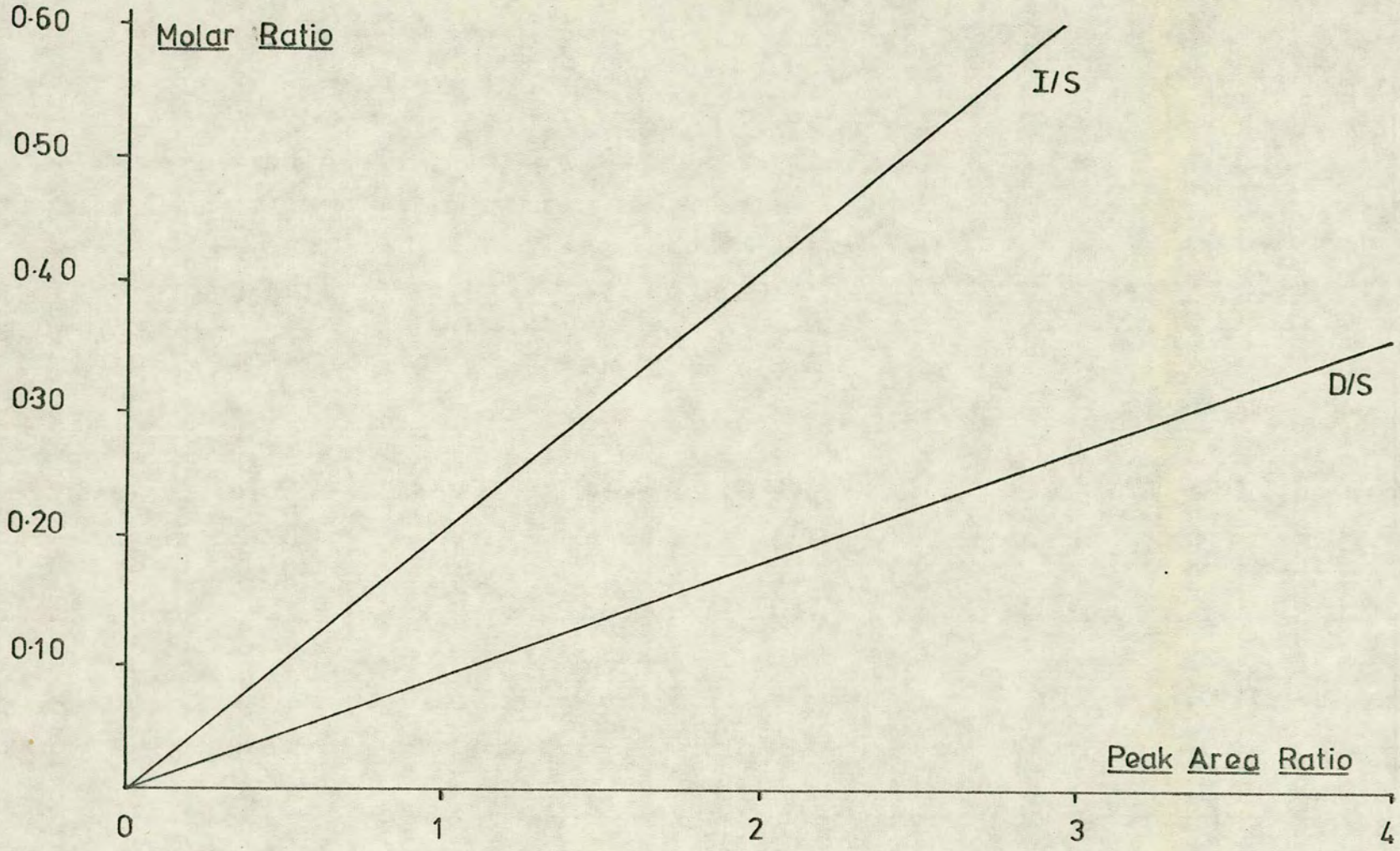

0·60
0·50
0·40
0·30
0·20
0·10
Molar Ratio
I/S
D/S
Peak Area Ratio
0
1
2
3
4

Fig. (xvi)

ii) Kinetics of the Isomerisation of 1,2,3,3a-Tetrahydro-10-phenylbenzo-[c]-cyclopenta-[f]-1,2-diazepine

In view of the similarity between glc and HSLC, it was expected that HSLC analysis could be quantified by the internal standard method as used in glc. A search for a suitable standard was therefore undertaken. Several different types of compound were tried viz. aza-aromatic compounds such as acridine and azaphenanthrenes, azafluoranthenes, azapyrenes, some aromatic nitrocompounds, some stable azocompounds and some esters. The best separation was obtained with diethyl phthalate which gave a peak in between and completely resolved from those due to the benzodiazepine and indazole (see fig. (xv)).

In a control experiment, two glass tubes, one containing diazepine, solvent and diethyl phthalate, the other containing solvent and diazepine only, were heated side by side in a solvent bath. These were sampled from time to time, and their liquid chromatograms obtained. These showed that the presence of diethyl phthalate did not affect the peak area ratios of diazepine:indazole in any way. This compound was therefore chosen as the internal standard and a calibration graph (fig. (xvi)) obtained using several synthetic mixtures of the indazole, the diazepine and diethyl phthalate.

The reaction vessel was a three-necked "Quickfit" test-tube, the central B19 joint being equipped with a mercury-sealed stirrer while one of the B10 side-arms was fitted with/...

Time (min)	Peak Area Ratio $I/_S$	$D/_S$	Molar Ratio $I/_S$	$D/_S$	mMoles I	D	Conc. I	D
0	-	3.449	-	0.308		0.588	-	0.0385
60	0.171	3.177	0.035	0.283	0.067	0.540	0.00446	0.0360
125	0.233	3.079	0.045	0.275	0.086	0.525	0.00574	0.0350
180	0.319	2.836	0.065	0.250	0.124	0.477	0.00826	0.0318
240	0.356	2.598	0.070	0.230	0.134	0.439	0.00894	0.0292
304	0.427	2.347	0.085	0.210	0.162	0.401	0.0108	0.0267
370	0.500	2.134	0.100	0.190	0.191	0.363	0.0127	0.0243
427	0.511	2.064	0.103	0.183	0.197	0.349	0.0131	0.0232
512	0.573	1.913	0.115	0.170	0.216	0.324	0.0144	0.0216
613	0.608	1.709	0.123	0.152	0.235	0.290	0.0157	0.0193
660	0.642	1.617	0.130	0.145	0.248	0.277	0.0165	0.0185
720	0.651	1.491	0.133	0.133	0.254	0.254	0.0169	0.0169
840	0.673	1.357	0.135	0.120	0.258	0.229	0.0172	0.0153
940	0.704	1.243	0.140	0.110	0.267	0.210	0.0178	0.0140
1080	0.725	1.155	0.146	0.104	0.279	0.199	0.0186	0.0133
1205	0.743	1.044	0.150	0.093	0.286	0.177	0.0191	0.0118
1410	0.721	0.979	0.145	0.088	0.277	0.168	0.0185	0.0112
1560	0.748	0.872	0.155	0.083	0.296	0.158	0.0197	0.0105
3000	0.751	0.552	0.155	0.050	0.296	0.095	0.0197	0.00634
3580	0.633	0.521	0.125	0.045	0.239	0.086	0.0159	0.00574
4320	0.595	0.417	0.120	0.035	0.229	0.067	0.0153	0.00446
5220	0.537	0.448	0.110	0.040	0.210	0.076	0.0140	0.00506
8260	0.368	0.272	0.075	0.025	0.143	0.047	0.00995	0.00314
9700	0.315	0.231	0.063	0.020	0.120	0.038	0.00800	0.00254

I = Indazole, D = Diazepine, S = Diethyl Phthalate

TABLE (3)

with a water-condenser and nitrogen inlet. The third neck was equipped with a rubber septum cap enabling the mixture to be sampled by microsyringe without entry of air to the system. The required weight of diazepine or indazole (150mg) was weighed into the reaction vessel and an accurately known weight of standard was added. Solvent sufficient to bring the volume of solution up to 15ml was added. The reaction vessel was then fitted with stirrer, condenser and septum cap and immersed in the thermostat bath at 131.4 $\pm$ 0.05°C. The stopclock was started on immersion of the reaction vessel, and 10μl samples were taken periodically. These were diluted immediately with 0.25ml of the HSLC solvent and analysed by HSLC. Since the use of HSLC in this way was a new and untried method, peak areas for the first run were calculated by three methods:

1) product of peak height and peak width at ½-height;
2) product of peak height and retention time[118] (which is proportional to peak area);
3) electronic integration.

The three methods gave different peak area ratios but the concentration-time graphs obtained were identical no matter which method was used. The calculations reported here utilised the electronic integrater.

The variations of concentration of indazole (55) and diazepine (5a) are given in tables (3) and (4) for reactions/...

Time	Peak Area Ratio		Molar Ratio		mMoles		Conc.	
	$I/_S$	$D/_S$	$I/_S$	$D/_S$	I	D	I	D
0	-	-	-	-	0.588	-	0.0385	-
65	1.388	0.094	0.28	0.01	0.540	0.0193	0.0366	0.00129
120	1.387	0.140	0.28	0.013	0.540	0.0251	0.0366	0.00167
180	1.345	0.270	0.273	0.025	0.527	0.0482	0.0352	0.00322
247	1.290	0.340	0.26	0.033	0.502	0.063	0.0334	0.00420
420	1.198	0.514	0.245	0.045	0.473	0.0868	0.0315	0.00578
630	1.148	0.577	0.233	0.050	0.449	0.0964	0.0300	0.00643
975	1.030	0.640	0.207	0.057	0.399	0.110	0.0266	0.00733
1455	0.952	0.769	0.192	0.070	0.370	0.135	0.0247	0.00900
1935	0.912	0.666	0.184	0.060	0.355	0.116	0.0236	0.00744
2670	0.890	0.584	0.180	0.053	0.347	0.102	0.0231	0.00680
3000	0.838	0.579	0.170	0.050	0.328	0.0964	0.0218	0.00643

TABLE (4)

reactions starting from diazepine (run (1)) and indazole (run (2)) respectively, and are displayed graphically in figs. (xvii) and (xviii).* The third curve in each of the two graphs is simply the sum of indazole and diazepine concentrations at any given time and is a measure of the disappearance of the azo-isomers.

Only three schemes viz. those of fig. (xiv) were considered for the data-fitting of the experimental results.

Two programmes viz. CHEK and CHEKMAT were used along with the IBM 370 computer to obtain rate constants and simulated reactions.[119] Both programmes are concerned with the simulation of chemical reaction kinetics in homogeneous solution according to the mass action laws. The CHEK programme carries out simulation, taking only a few seconds for a typical run. The CHEKMAT programme can also adjust the numerical values of specified parameters (usually rate constants) to give best fit between the results of a simulation run and observed time courses of selected concentrations, executing simulation runs as a subprocess. Programme CHEKMAT can be used for simulation runs in place of programme CHEK if desired.

Each programme contains a first phase in which the chemical equations, whose kinetics are to be simulated, are/...

* See sub-section (iii) below

are read. They are expressed in a free format language, which within the limitations of the computer input character set is very similar to that which chemists normally use in expressing chemical reactions; it provides facilities for setting the values of rate constants and, if desired, initial values for the concentrations of the chemical species.

After this, the programme alternately reads commands describing the action required of it, and executes this action, returning to the command reading phase on completion. The action may range from printing the value of some concentration, or setting a new value for it or for a rate constant, to carrying out a complete simulation run on the equations; in the case of programme CHEKMAT it may include carrying out a parameter fitting run, involving many simulation runs.

Specification of the chemical equations in the programme determines the differential equations which will be solved. For example, consideration of scheme (A) of fig. (xiv) leads to solution of the differential equations:

$$-\frac{d[D]}{dt} = (k_1 + k_3)[D] - k_2[I] \quad - (1)$$

$$-\frac{d[I]}{dt} = (k_2 + k_4)[I] - k_1[D] \quad - (2)$$

In order to effect solution of these equations and obtain simulation runs, it is only now necessary to specify the initial/...

initial concentrations of the various chemical species.

The best fit rate constants obtained from runs (1) and (2) using scheme (A) are shown in table (5) along with the averaged value and the calculated equilibrium constant. The first point of note concerning these results is the fact that agreement between the two runs was not particularly good. This was possibly due to the fact that the temperature control was better in run (2) *viz*. 134.1 $\pm$ 0.05° as opposed to 134.1 $\pm$ 0.3°C in run (1). However, these rate constants were used in conjunction with the CHEK programme to predict the concentration *vs* time curves for experiments starting with diazepine and with indazole. Figures (xix), (xx), (xxi), (xxii) and (xxiii), (xxiv) show the simulated reactions* pertaining to run (1) best fit data, run (2) best fit data and averaged best fit data respectively, superimposed on the experimental data points. From these, it may readily be seen that the computer-simulation using run (1) data (fig. (xix) and (xx)) seems to fit both reactions fairly well whereas, using run (2) and the averaged data, the fit is good for indazole decomposition only.

Scheme (B) (fig. (xiv)) in which k_4 was set to zero, *i.e.* all decomposition occurring *via* the diazepine, was considered next. Using the same computer technique as before/...

* See sub-section (iii) below

	Run (1) data	Run (2) data	Averaged Data
k_1	1.1184×10^{-3}	1.6765×10^{-3}	1.397×10^{-3}
k_2	4.3104×10^{-4}	5.4218×10^{-4}	4.866×10^{-4}
k_3	1.9501×10^{-4}	6.8778×10^{-5}	1.313×10^{-4}
k_4	1.0957×10^{-4}	1.0687×10^{-4}	1.082×10^{-4}
$K = k_1/k_2$	2.59	3.09	2.87

TABLE (5)

	Run (1) data	Run (2) data	Averaged Data
k_1	1.1075×10^{-3}	1.529×10^{-3}	1.3100×10^{-3}
k_2	5.5843×10^{-4}	6.1981×10^{-4}	5.870×10^{-4}
k_3	3.2600×10^{-4}	4.9614×10^{-4}	4.13×10^{-4}
k_4	0	0	0
$K = k_1/k_2$	1.98	2.48	2.23

TABLE (6)

	Run (1) data	Run (2) data	Averaged Data
k_1	1.2151×10^{-3}	1.7198×10^{-3}	1.4675×10^{-3}
k_2	4.0316×10^{-4}	5.3352×10^{-4}	4.6834×10^{-4}
k_3	0	0	0
k_4	2.3195×10^{-4}	1.2144×10^{-4}	1.7670×10^{-4}
$K = k_1/k_2$	3.01	3.03	3.01

TABLE (7)

before, the best fit rate constants were determined as shown in table (6) along with the derived equilibrium constants. Using these data, computer calculation gave the graphs, corresponding to run (1), run (2) and averaged best fit data, shown in figs. (xxv), (xxvi), (xxviii), (xxviii) and (xxix), (xxx),* but here, there appeared to be more discrepancies between calculation and experimental data.

Scheme (C) (fig. (xiv)) in which k_3 was set to zero, i.e. all decomposition occurring via the indazole, was the third and final consideration. Best fit rate constants and the derived equilibrium constants are given in table (7) and the computer simulated curves are shown in figs. (xxxi), (xxxii), (xxxiii), (xxxiv) and (xxxv), (xxxvi).* These showed least agreement with the experimental data. For this reason, scheme (C) could probably be ruled out as a possible mechanism. However, it was not really possible to decide between schemes (A) and (B) since the calculations for both of these schemes showed some agreement with the experimental data. Despite this, it can be deduced from this exercise that the isomerisation of (5a) to (55) or (55) to (5a) occurs at a faster rate, by a factor of between about 5 and 10, than the decomposition of the azo-isomers occurs. Furthermore, it would appear/...

* See sub-section (iii) below

appear that the equilibrium constant for the isomerisation of (5a) to (55) lies within the range of values 2-3.

In order to complete this study, a series of reactions at various temperatures require to be carried out. This would allow calculation of the energy and entropy of activation for the reaction, knowledge of which should provide a better indication of the mechanism in operation. This work is currently being undertaken by another member[120] of the group.

In conclusion, the use of computer simulation did not provide an unambiguous solution to the question of the mechanism of the isomerisation and subsequent decomposition of (5a) and/or (55) due to the limited amount of data available. However, the preliminary results obtained indicate that the use of HSLC for analysis and the computer simulation technique may well be of great value in investigations involving equilibria and decompositions of labile compounds.

iii) Experimental and Computer Simulated Kinetics Graphs

This section contains the graphical representations of the two kinetics runs - figs. (xvii) and (xviii) - and the eighteen computer simulated plots described in the previous section - figs. (xix) - (xxxvi).

Key to Graphs

Abscissa	-	Time in minutes
Ordinate	-	Concentration in moles per litre x 10^3
⊙	-	Diazepine concentration, [D]
x	-	Indazole concentration, [I]
Δ	-	[D] + [I] (figs. (xvii) and (xviii) only)

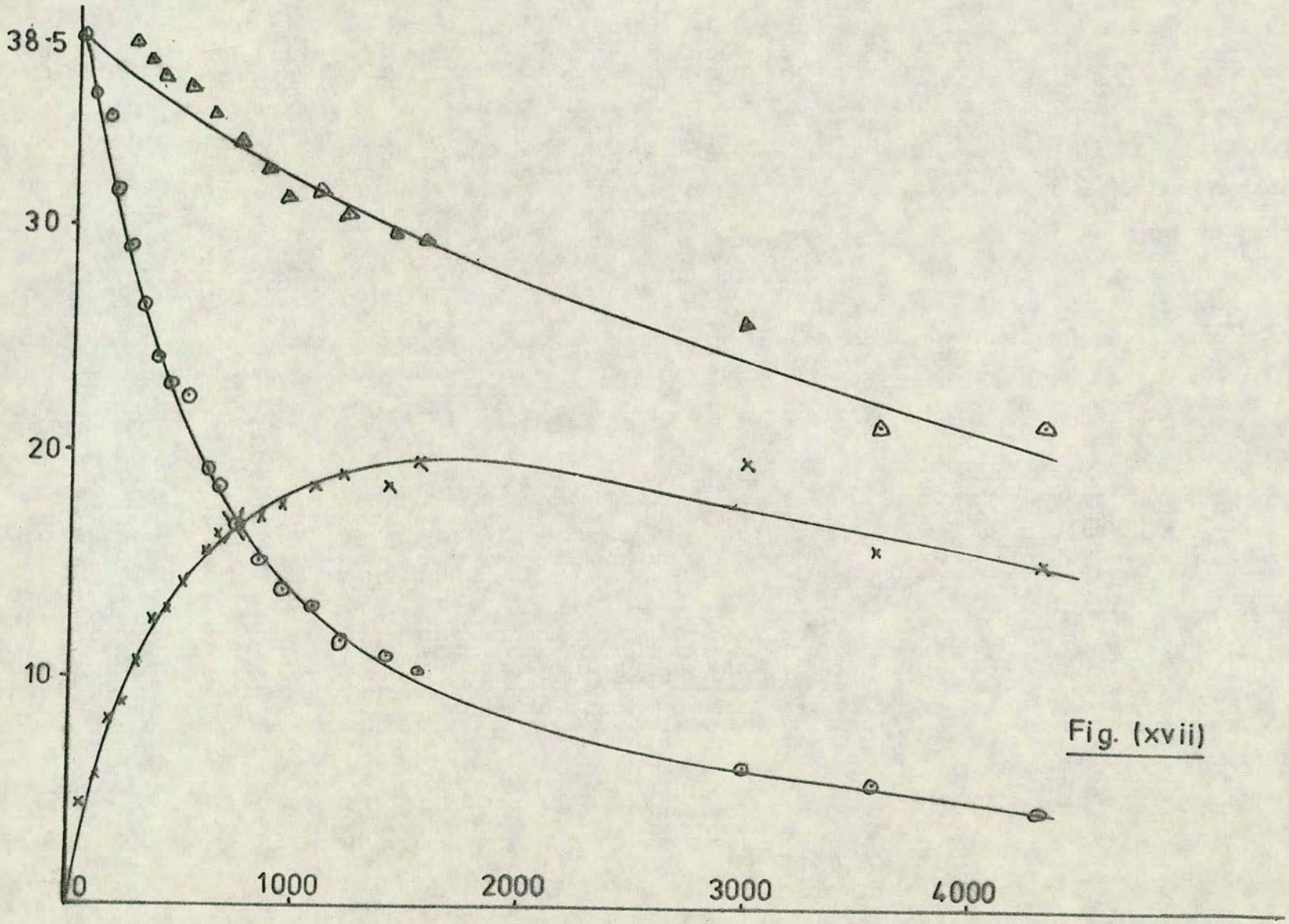


Fig. (xvii)

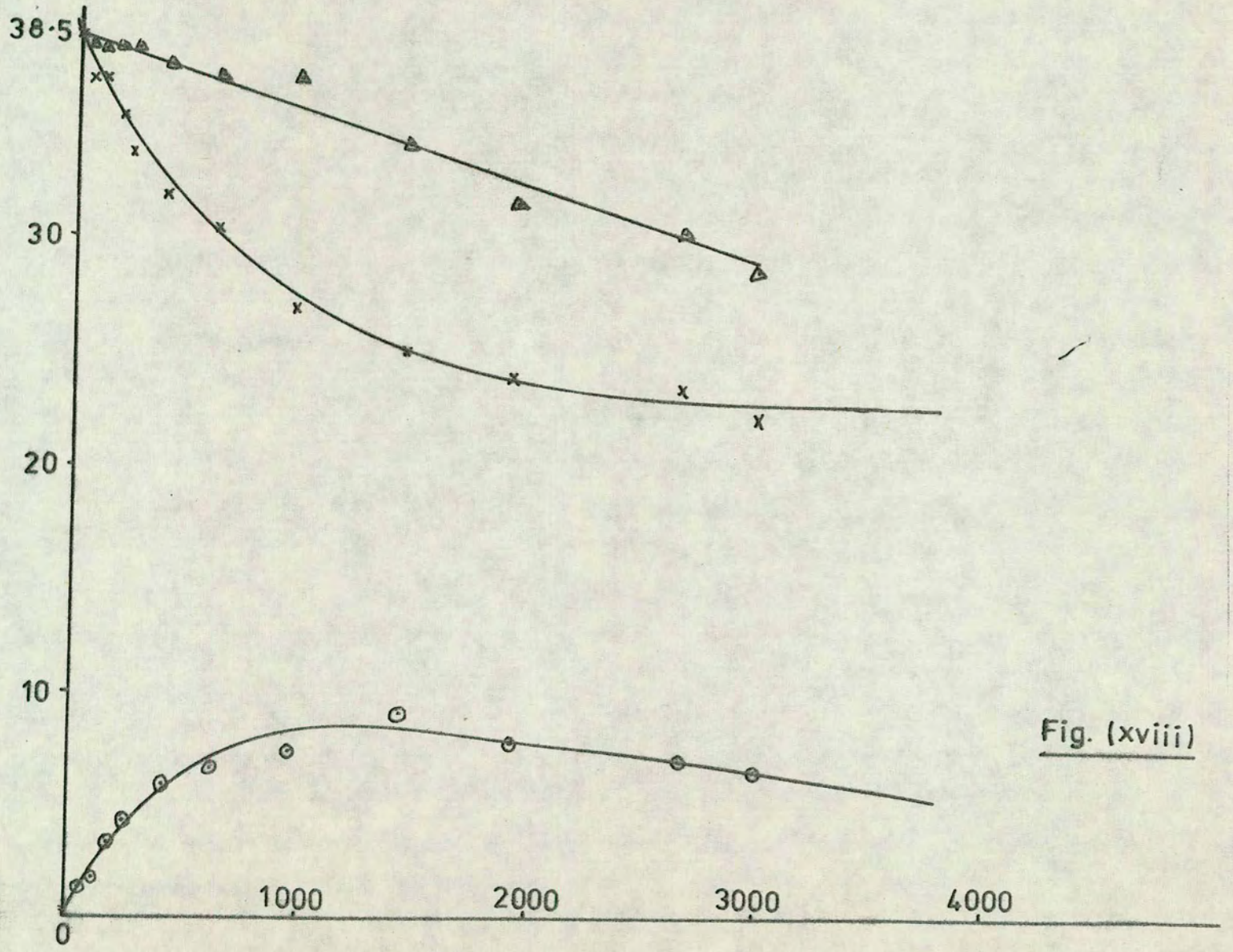


Fig. (xviii)

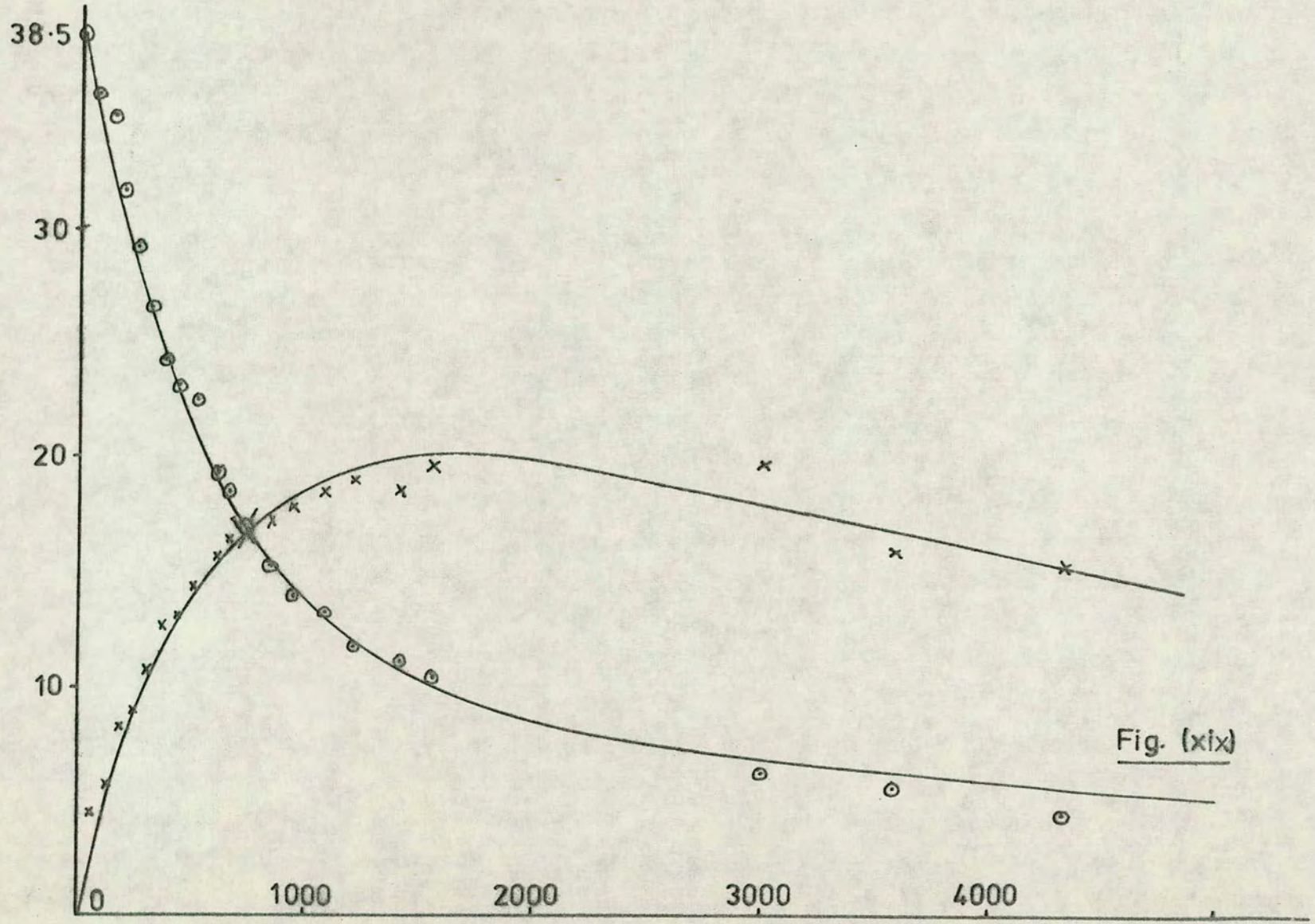


Fig. (xix)

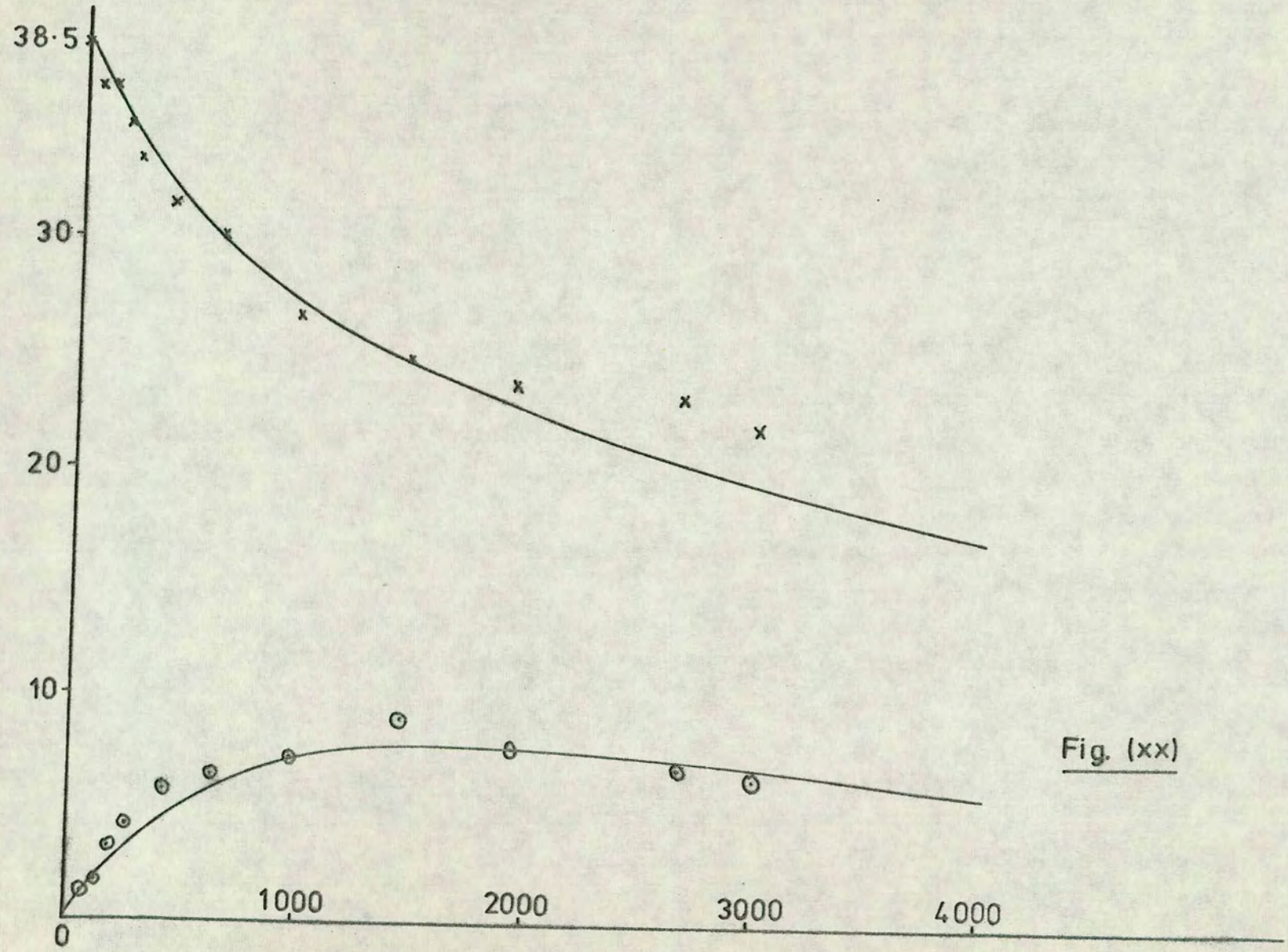


Fig. (xx)

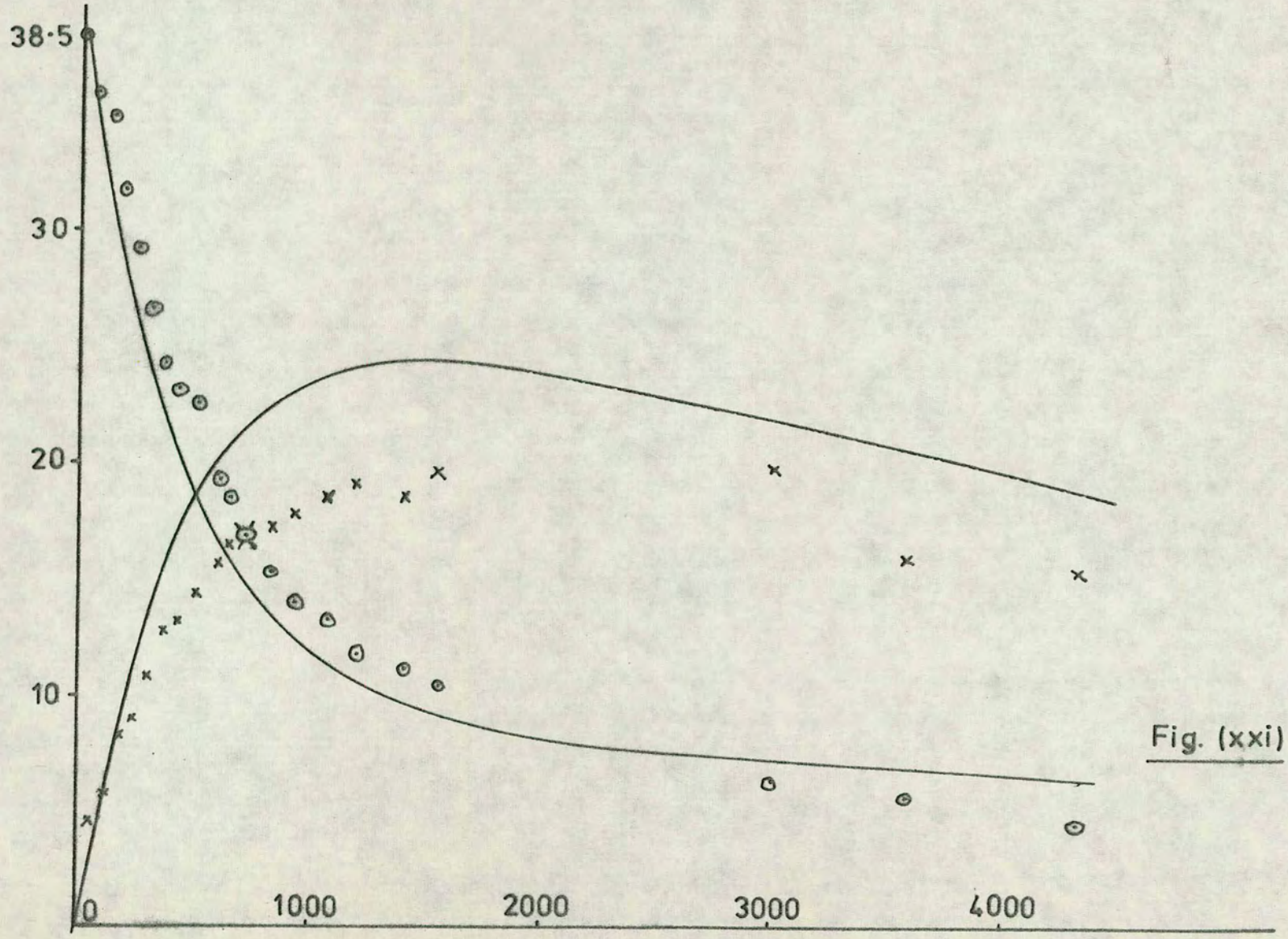
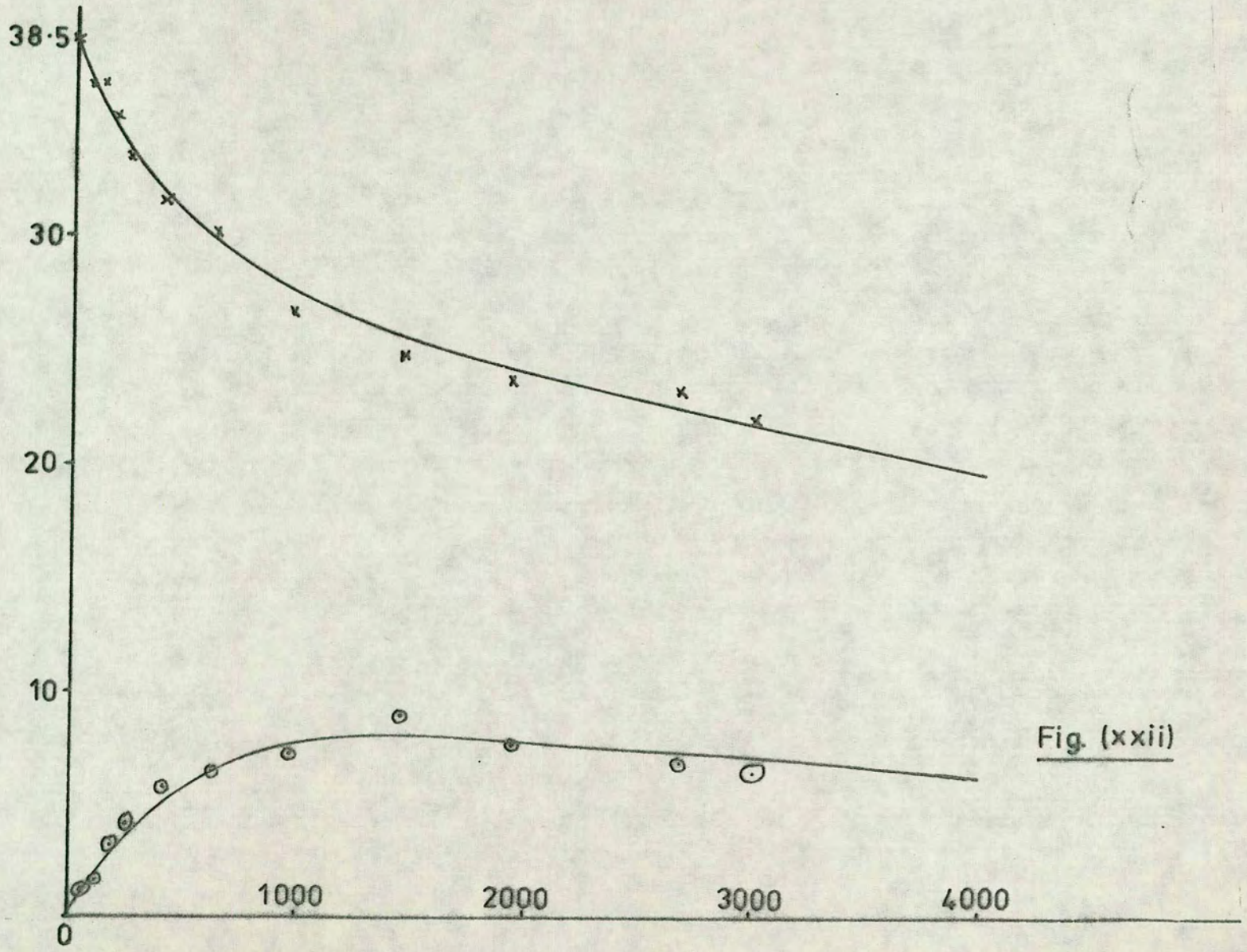


Fig. (xxi)



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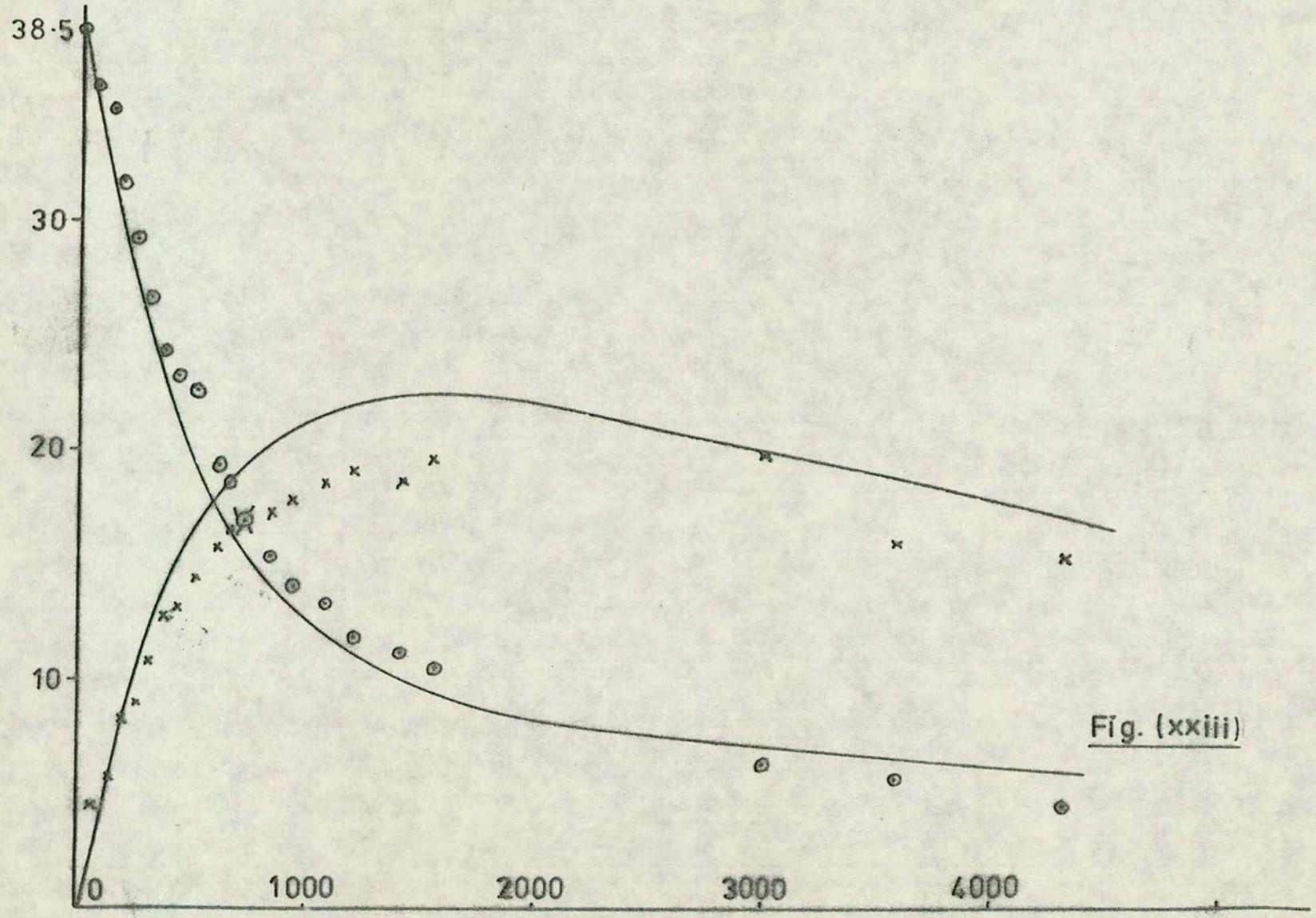

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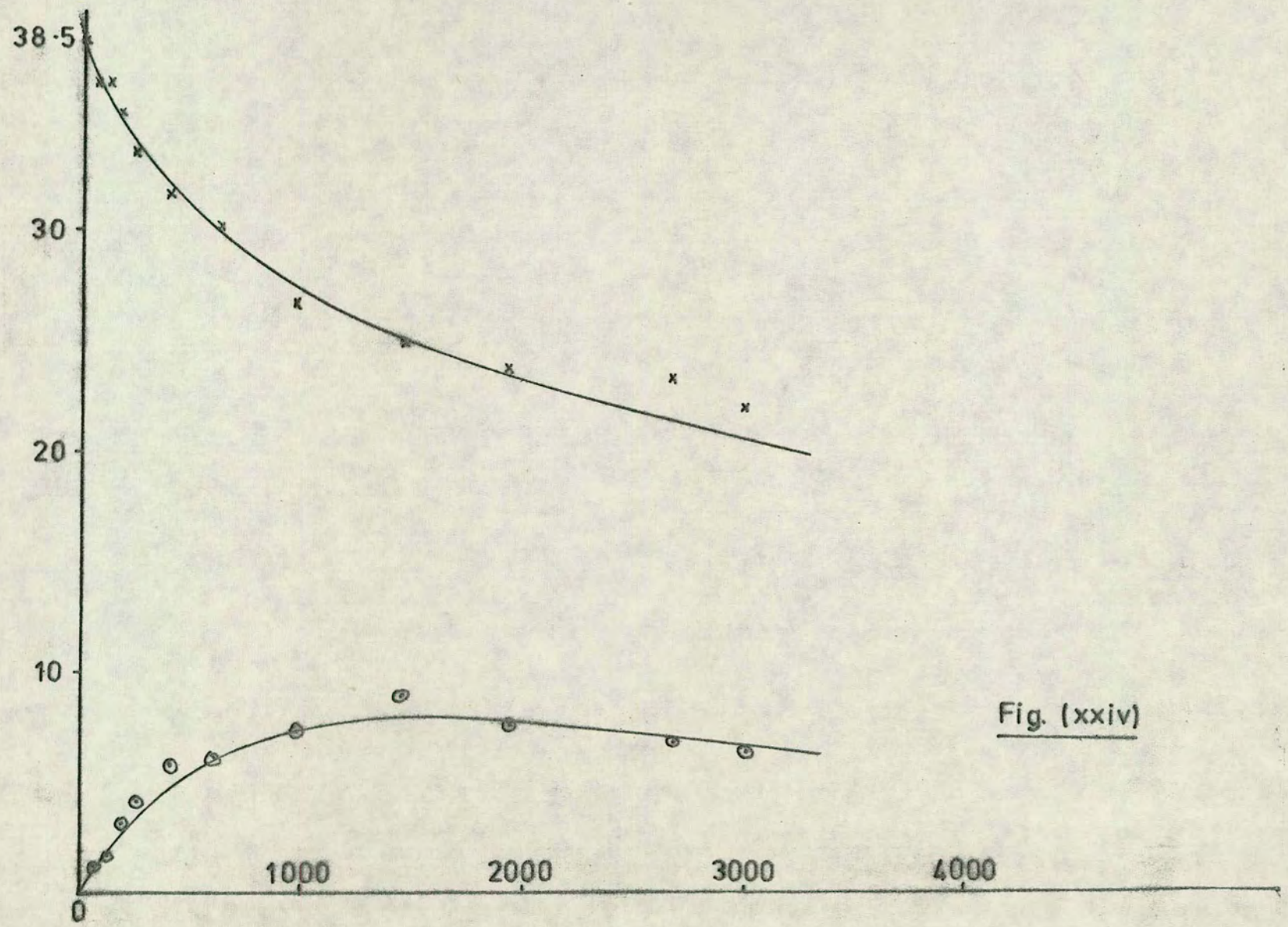

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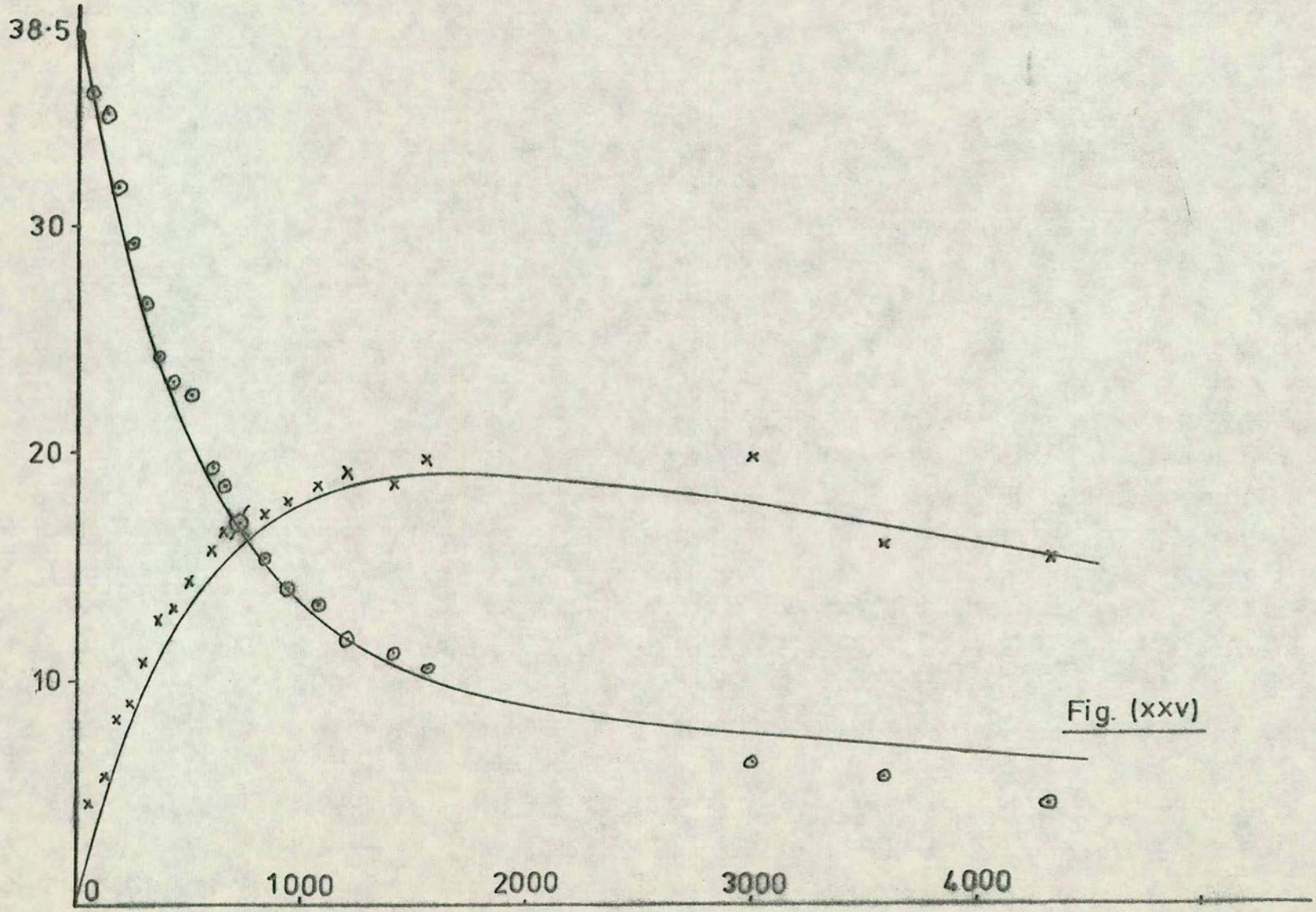

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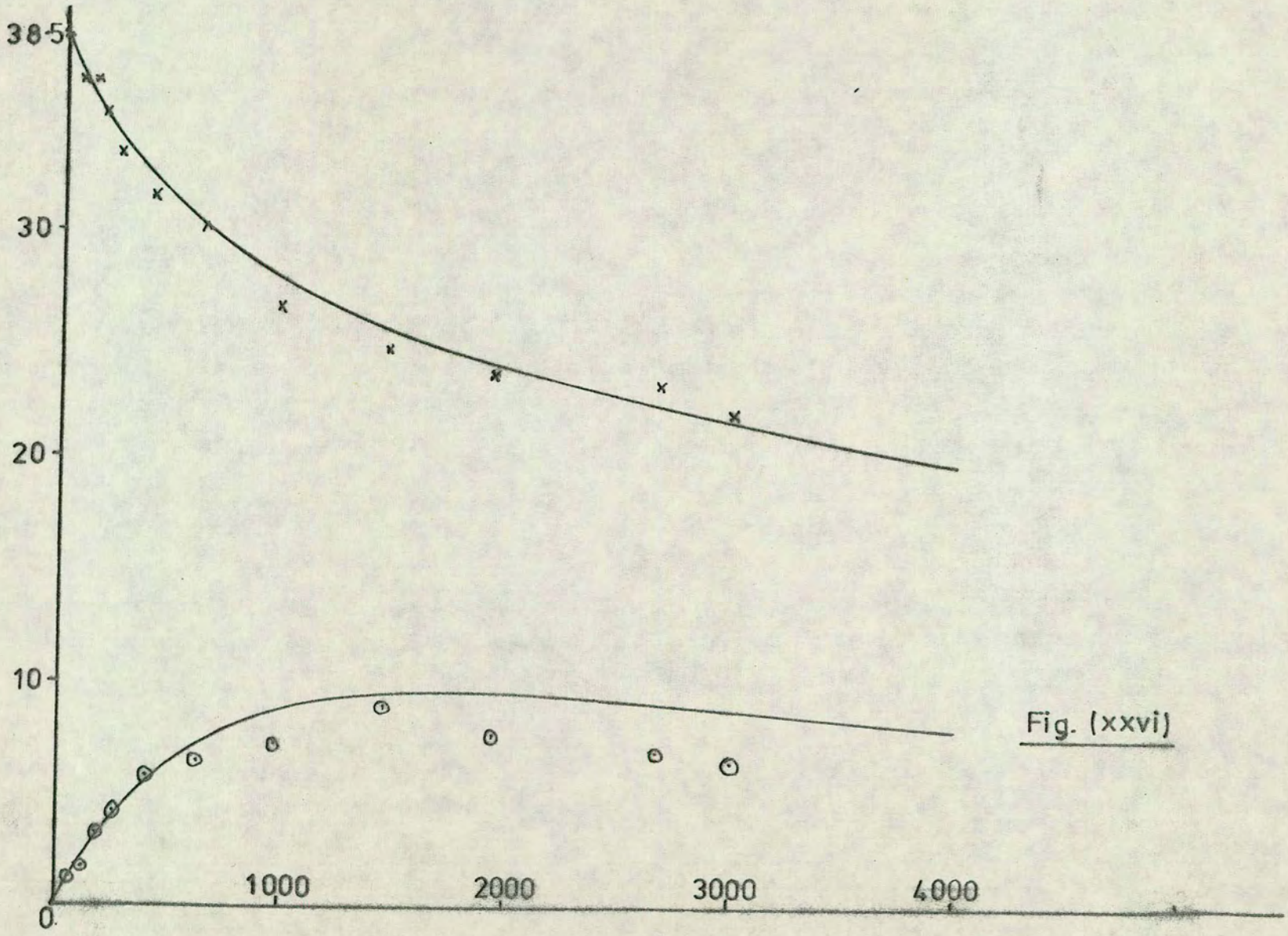

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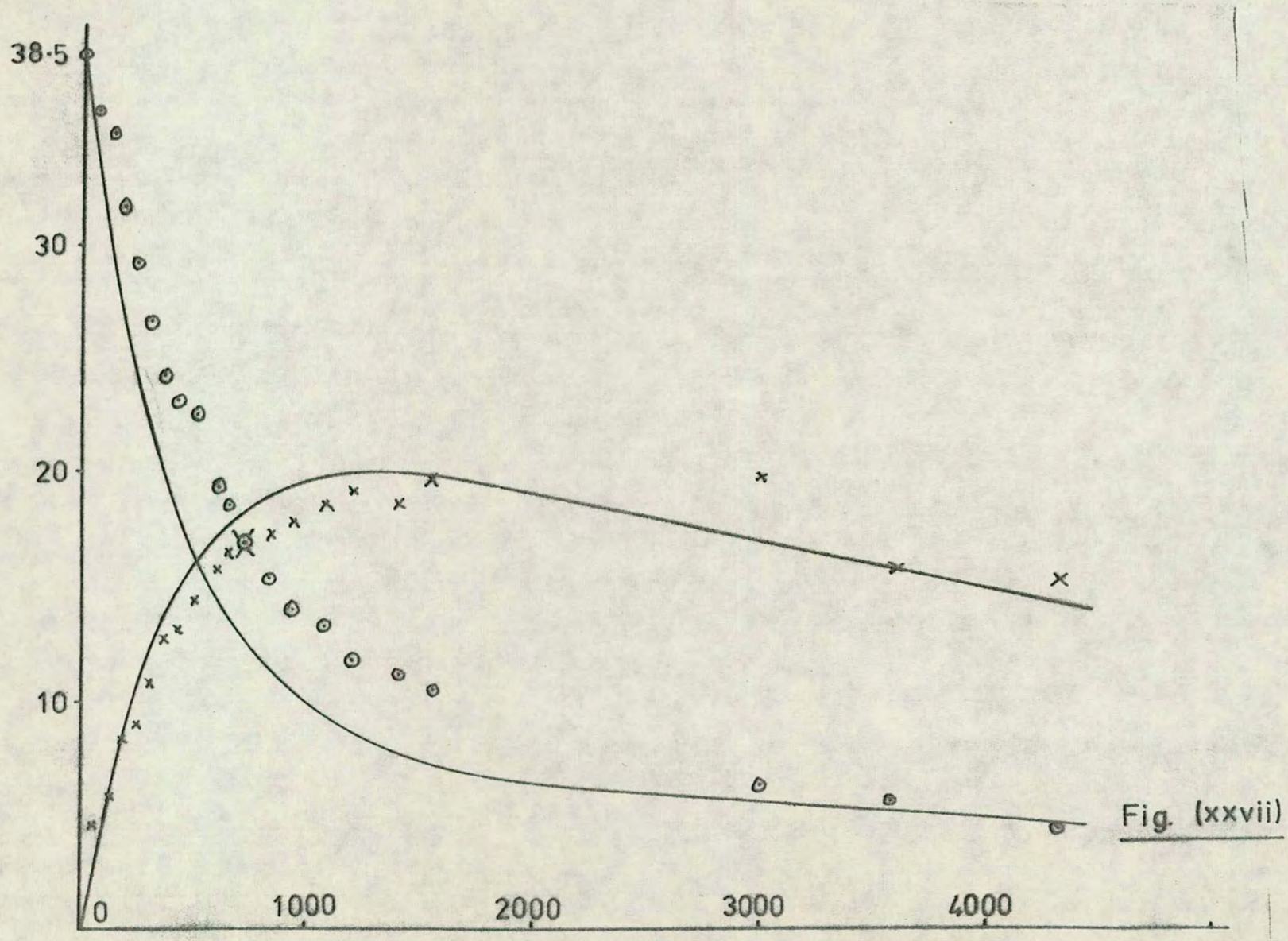

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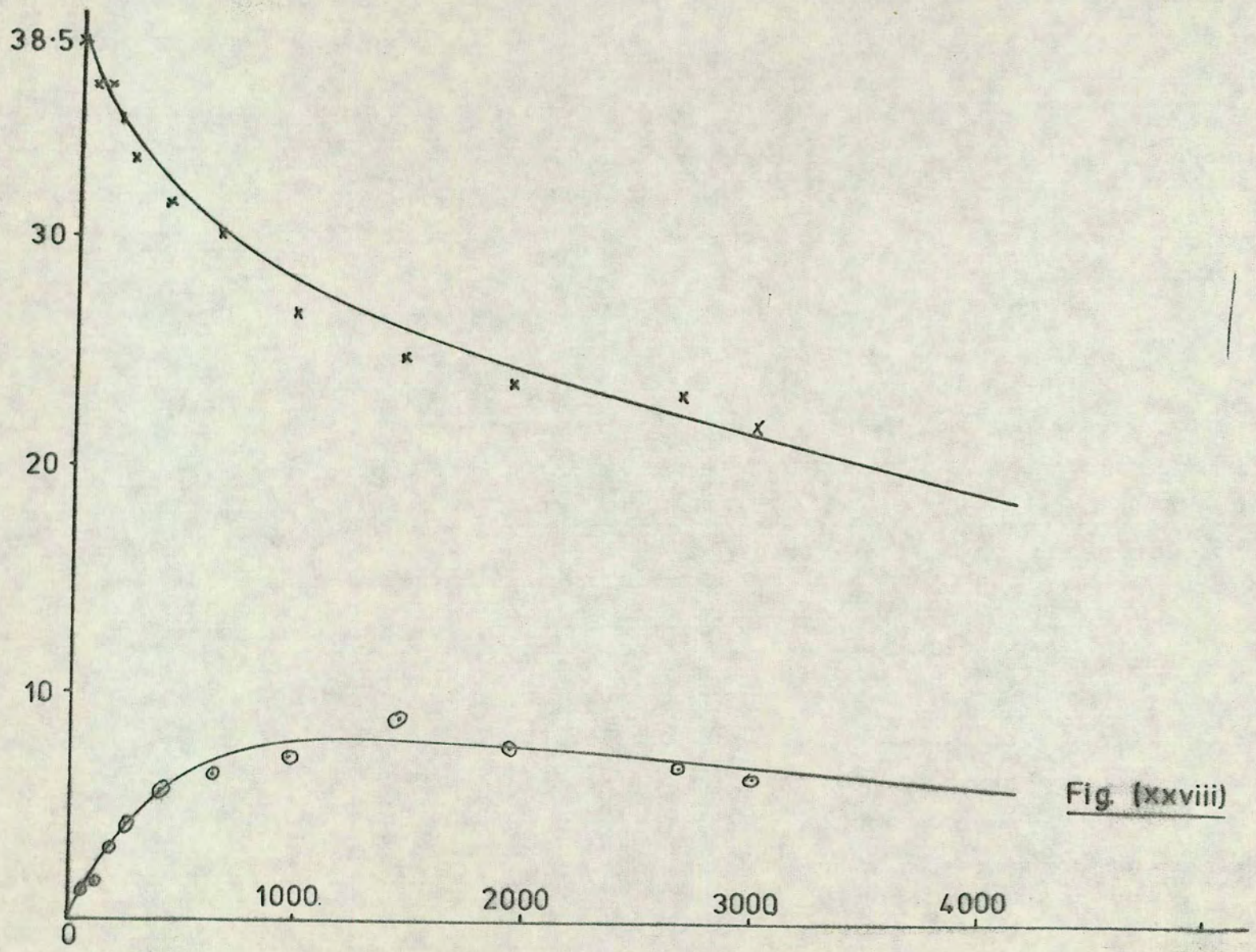
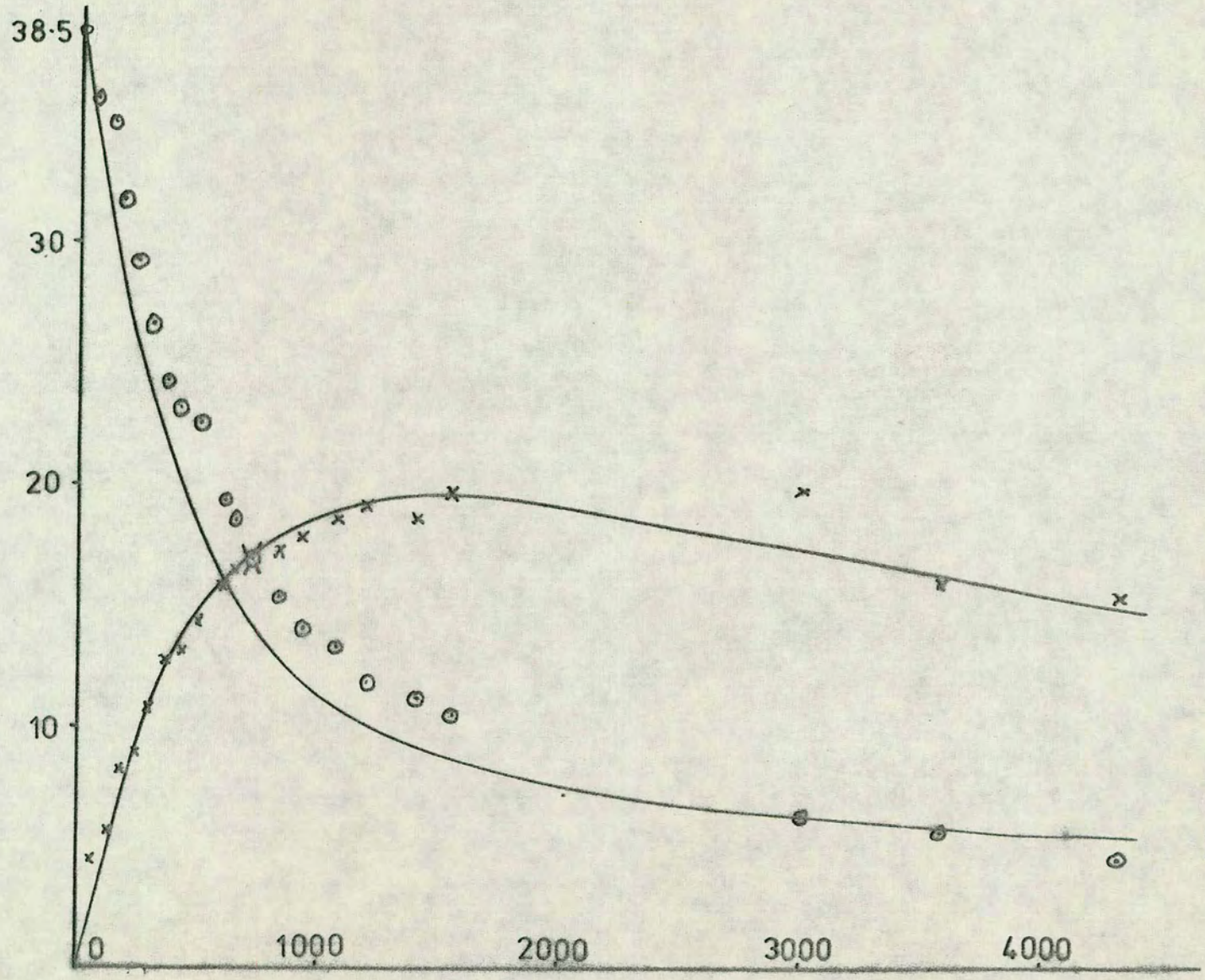


Fig. (xxviii)



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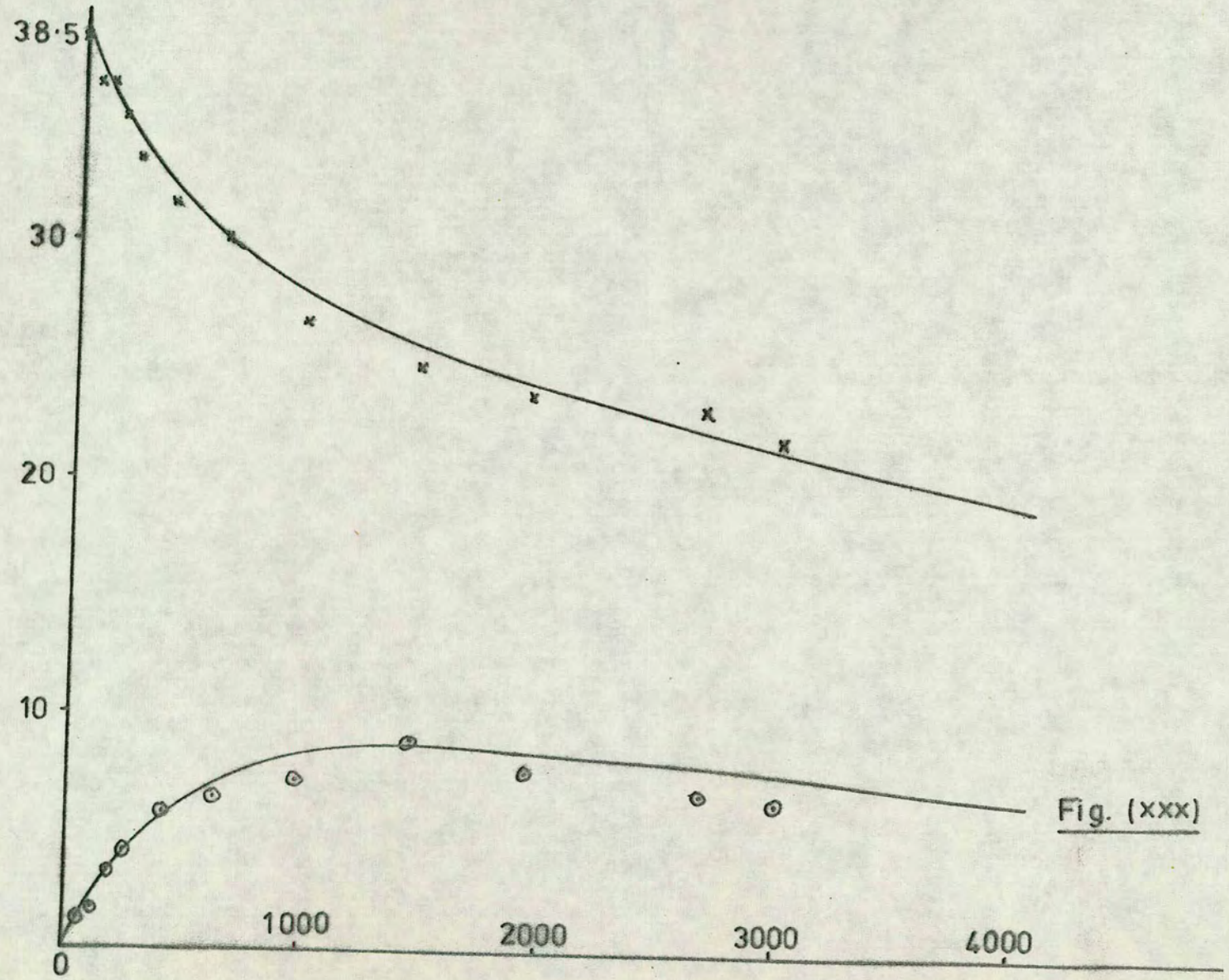

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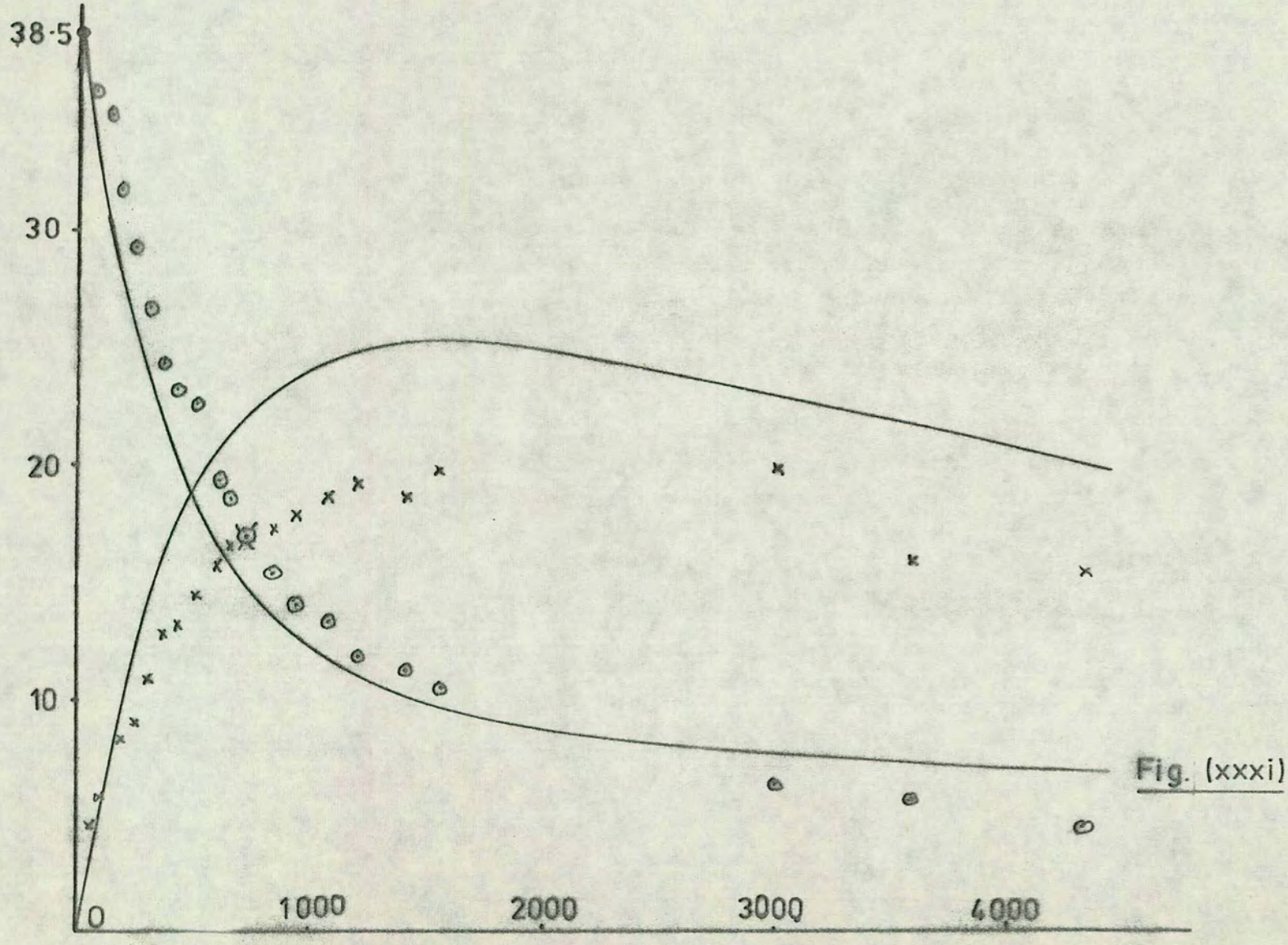

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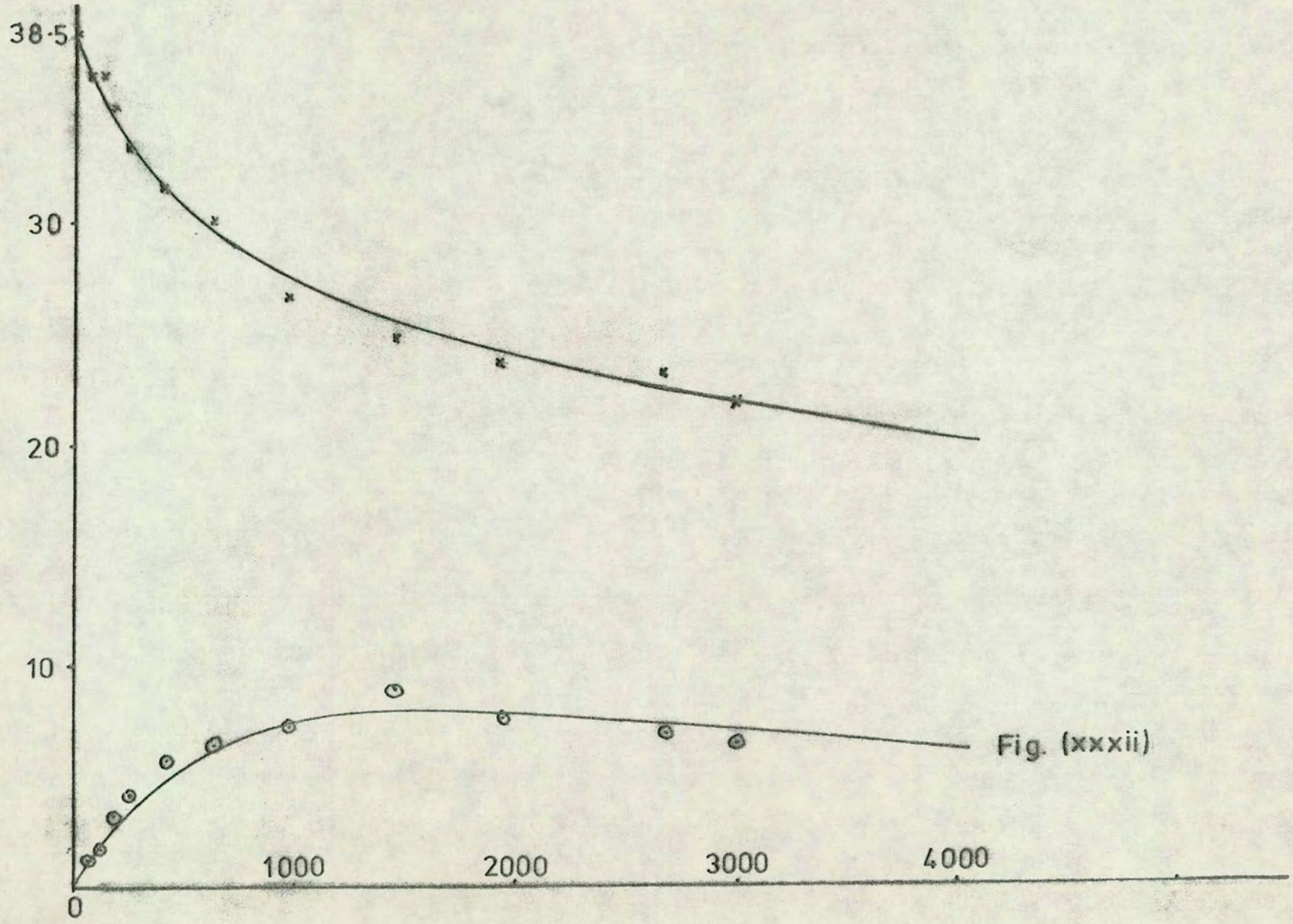
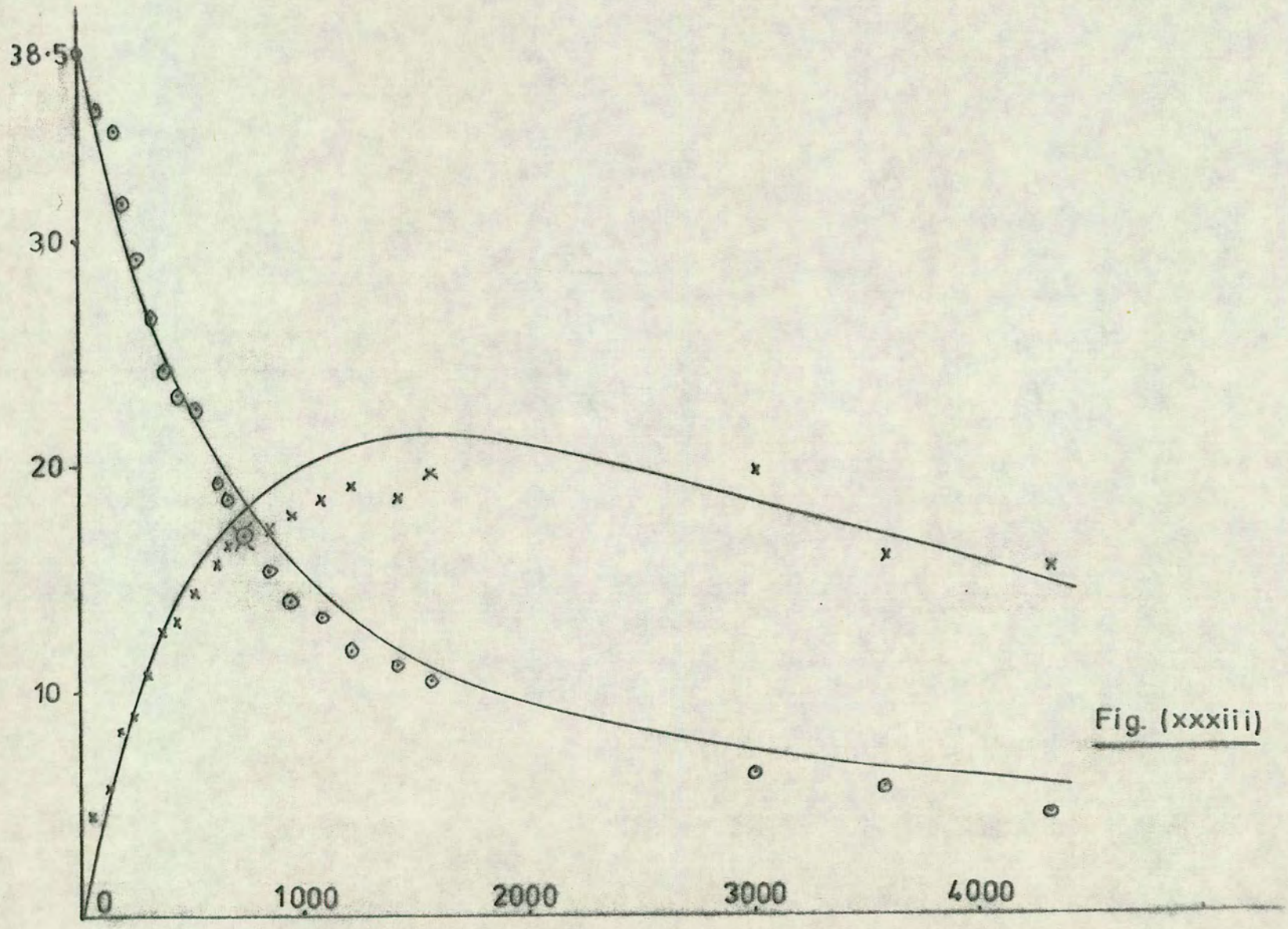


Fig. (xxxii)



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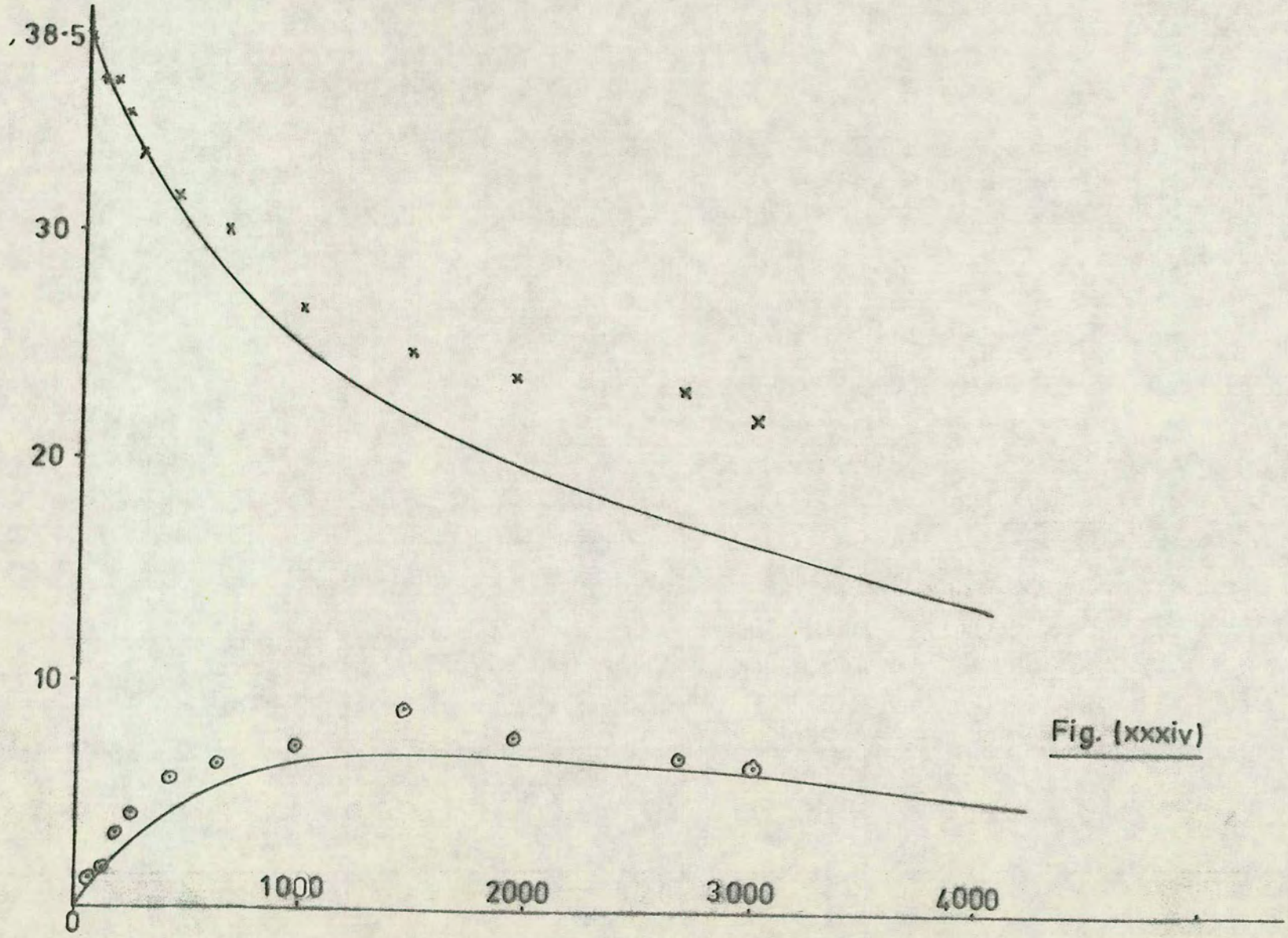

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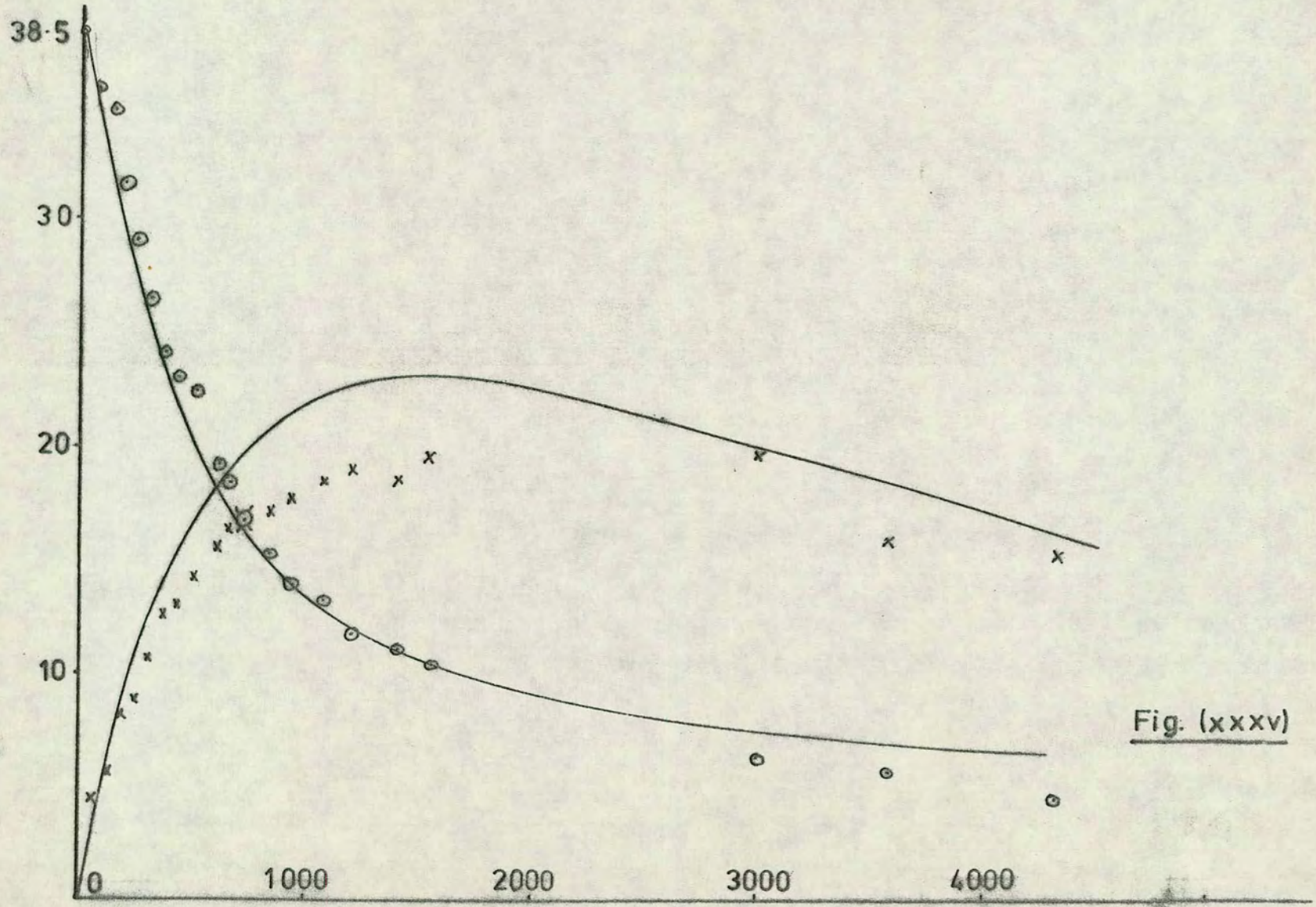


Fig. (xxxv)

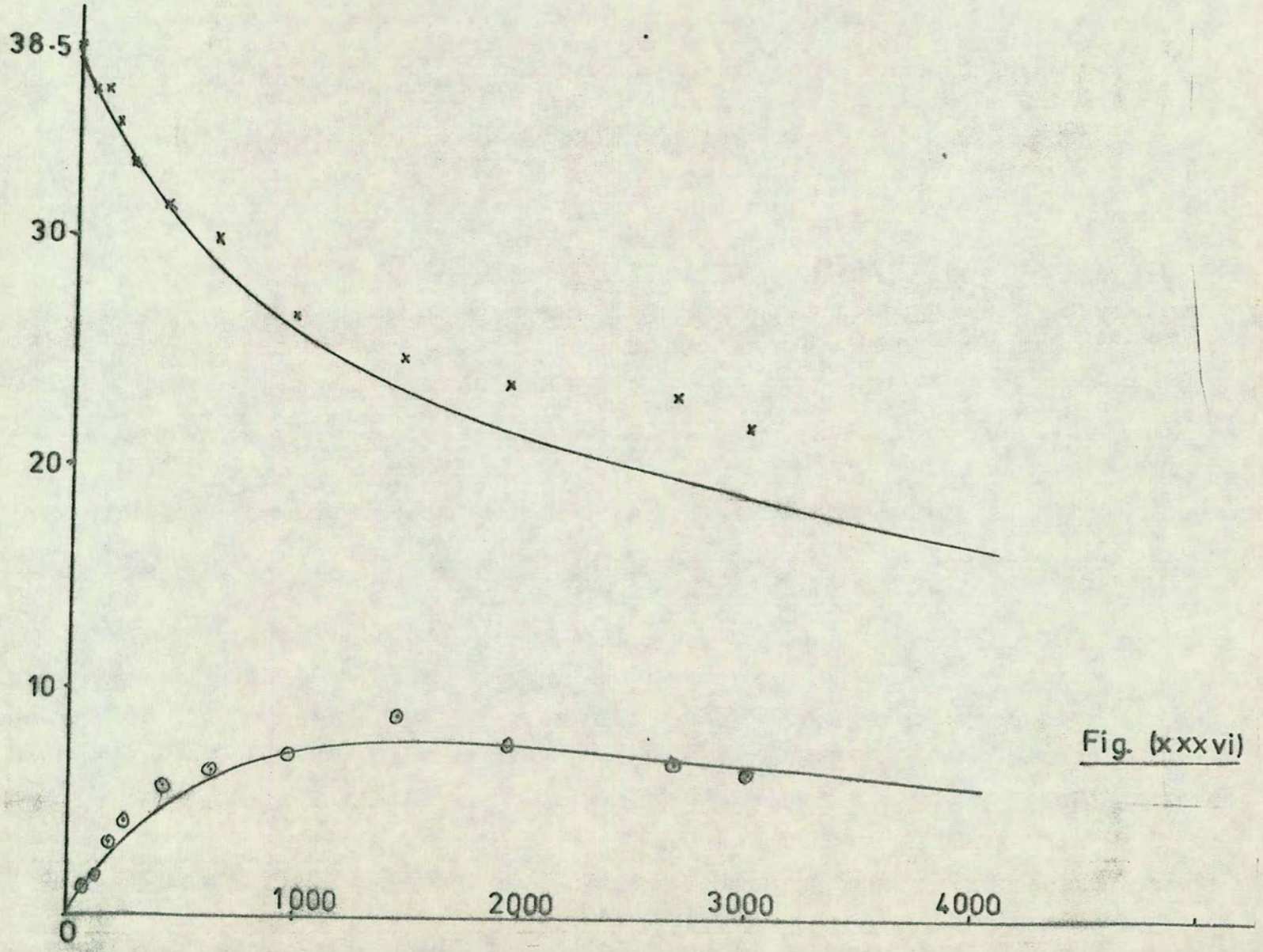
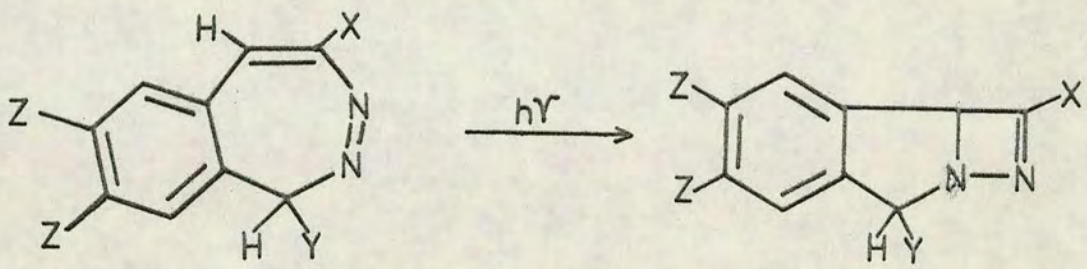


Fig. (xxxvi)

VI Photolysis of 3H-1,2-Benzodiazepines and their Tosylhydrazone Salt Precursors

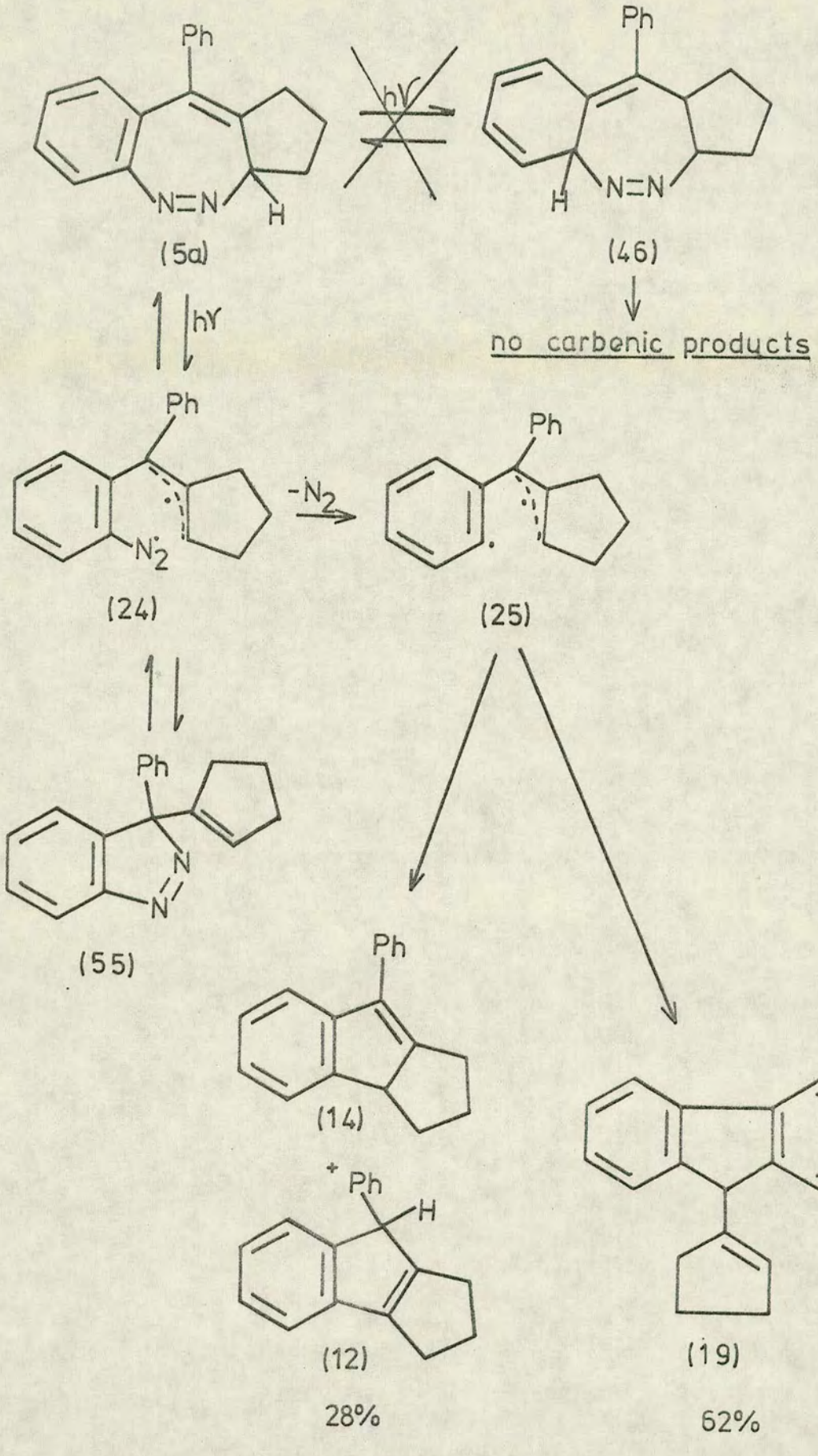
a) Photolysis of 3H-1,2-Benzodiazepines

1H-2,3-Benzodiazepines of general structure (61) have been shown[121] to retain nitrogen on irradiation, and to form the novel isomeric products (62):



(61) (62)

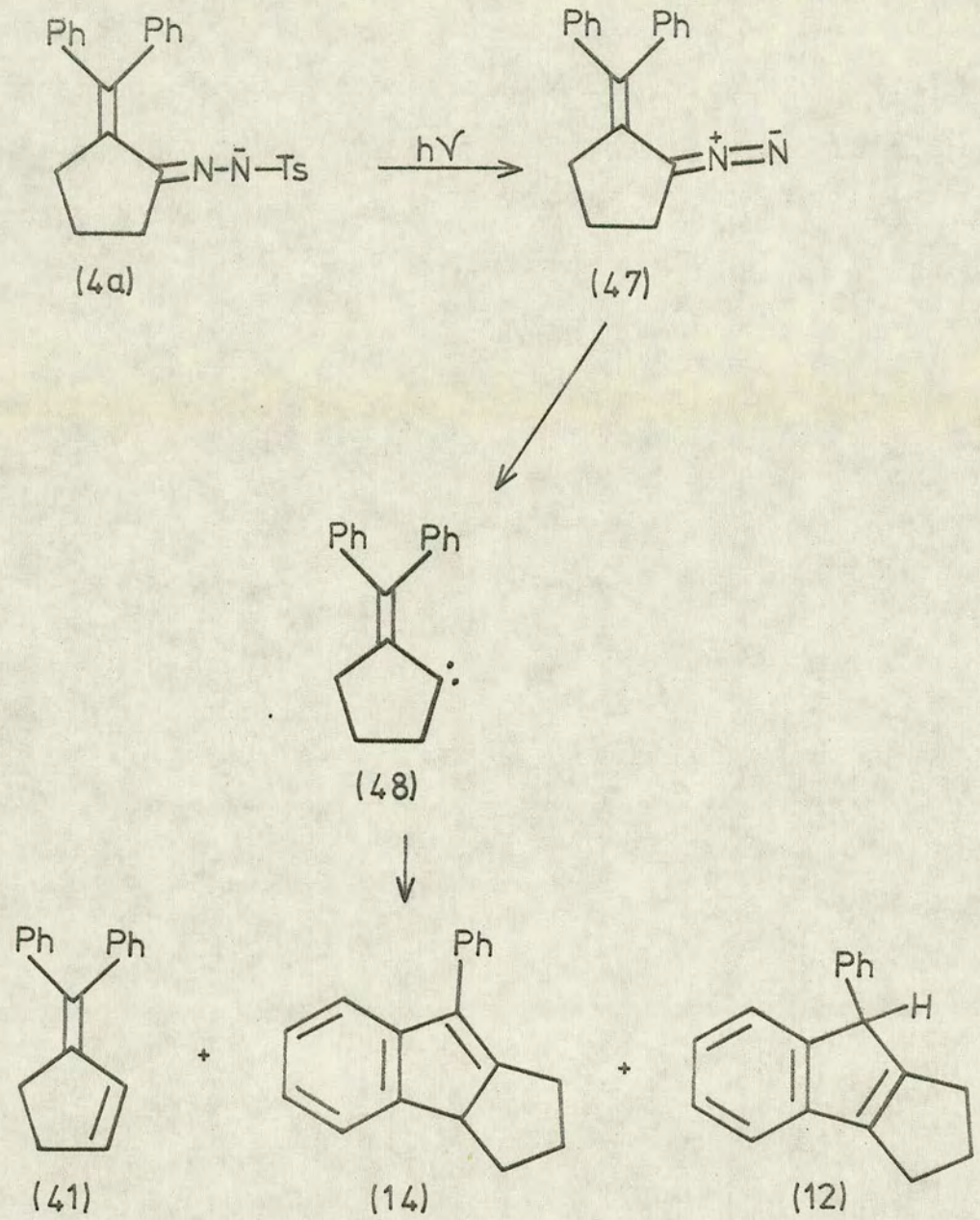
In view of this observation, and the isomerisation of (5a) described above, it was now of interest to examine the photolysis of 1,2,3,3a-tetrahydro-10-phenylbenzo-[c]-cyclopenta-[f]-1,2-diazepine (5a) and its dimethyl analogue (5b) to see whether nitrogen would be eliminated or retained. To this effect, the benzodiazepines (5a) and (5b) were photolysed in dry DME solution using a medium pressure Hanovia lamp, the radiation being filtered through a pyrex jacket. The reaction mixture of (5a) was sampled every few minutes by microsyringe, and high speed liquid chromatograms obtained. These showed quite clearly the growth of two peaks (corresponding to hydrocarbon products and indazole) as the diazepine/...



Scheme (27)

diazepine gradually disappeared. At no stage in the reaction was there complete conversion to the indazole isomer suggesting that this compound was again formed in an equilibrium process. No kinetics measurements were attempted.

After 1h, the reaction was observed to have gone to completion, there being only hydrocarbon products. After removal of the solvent, the mixture was hydrogenated and the products separated by column chromatography. These were then identified by their glc retention times (2½% OV1, 200°), glc-mass spectra and nmr spectra as 1-phenyl-cyclopenta-[b]-indane (28%) and 9-cyclopentyl-fluorene (62%) cf 32% and 45% respectively in the gas phase reaction at 400°. No diphenylmethylcyclopentane (38) was observed. This indicates, that, on photolysis, reaction occurs only via the diradical mechanism, there being no cyclic reversion to the diazo-compound (47) with subsequent formation of carbenic products (scheme (27)). The different product ratios in the thermal and photochemical reactions is presumably due to the different energies of the intermediate diradical. In a reaction which was benzophenone sensitised, irradiation of (5a) gave a complex mixture of products (glc; 1% SE30, 170°) which was not analysed further. This observation provides evidence against a triplet state intermediate in the above reactions. Photolysis of (5b) followed the same pattern to that above, giving only cyclopentaindane and/...



Scheme (28)

and cyclopentylfluorene products on hydrogenation. The product ratio was 1:2 respectively cf 1:1.4 in the gas phase reaction at 400°. This is in complete agreement with the unsubstituted case.

b) Photolysis of 2-Diphenylmethylenecyclopentanone Toluene-p-sulphonylhydrazone Sodium Salt

It has been shown*, that tosylhydrazone salts, on photolysis afford the corresponding diazo-compounds which often react via nitrogen-loss to give carbenes, which are the precursors to the observed products. In order to determine the product-forming properties of 2-diphenylmethylenecyclopentylidene (48), the photolysis of the sodium salt of 2-diphenylmethylenecyclopentanone tosylhydrazone (4a) was investigated. It should be noted that the carbene (48) is not readily accessible from (4a) by a thermal method since the diazocompound precursor to (48) tends to react via an electrocyclic ring closure to give the benzodiazepine (5a) in preference to nitrogen-loss. However, it was thought that (48), prepared by a photolytic method, would give rise to the products (12) and/or (14) and (41) which were obtained in the solution phase decomposition of (5a), as depicted in scheme (28).

The sodium salt was prepared and dried in the usual manner/...

* See Introduction

manner in the photochemical reactor. Since carbenes are known[122] to react with molecular oxygen to give ketones, reactions were carried out under an atmosphere of nitrogen which had been deoxygenated by passing through a solution of pyrogallic acid,[123] and dried by passing through a column of fresh phosphorous pentoxide. Irradiation for 1h in DME at room temperature gave complete decomposition. The hydrocarbon products were identified by their glc retention times (1% SE30, 175°) and their glc-mass spectra after hydrogenation.

Benzophenone-sensitised photolysis followed by hydrogenation gave (diphenylmethyl)cyclopentane (38) and 1-phenyl-1H-cyclopenta-[b]-indane (8) in the ratio 1:5. When the reaction was pyrex-filtered, the overall yield was 20% whereas photolysis through quartz gave a 33% yield. Yields were determined after chromatographing the reaction mixture on a dry alumina column to remove the photosensitiser. No matter how carefully this reaction was carried out, the maximum yield of hydrocarbon products was never more than 33%.

In a benzophenone-sensitised photolysis, most of the radiation is absorbed by the sensitiser, and this is then transferred to the reactant molecules on collision. Since benzophenone is a triplet sensitiser, then collision with reactant molecules gives a transferance of triplet energy, and hence a triplet state intermediate. This/...

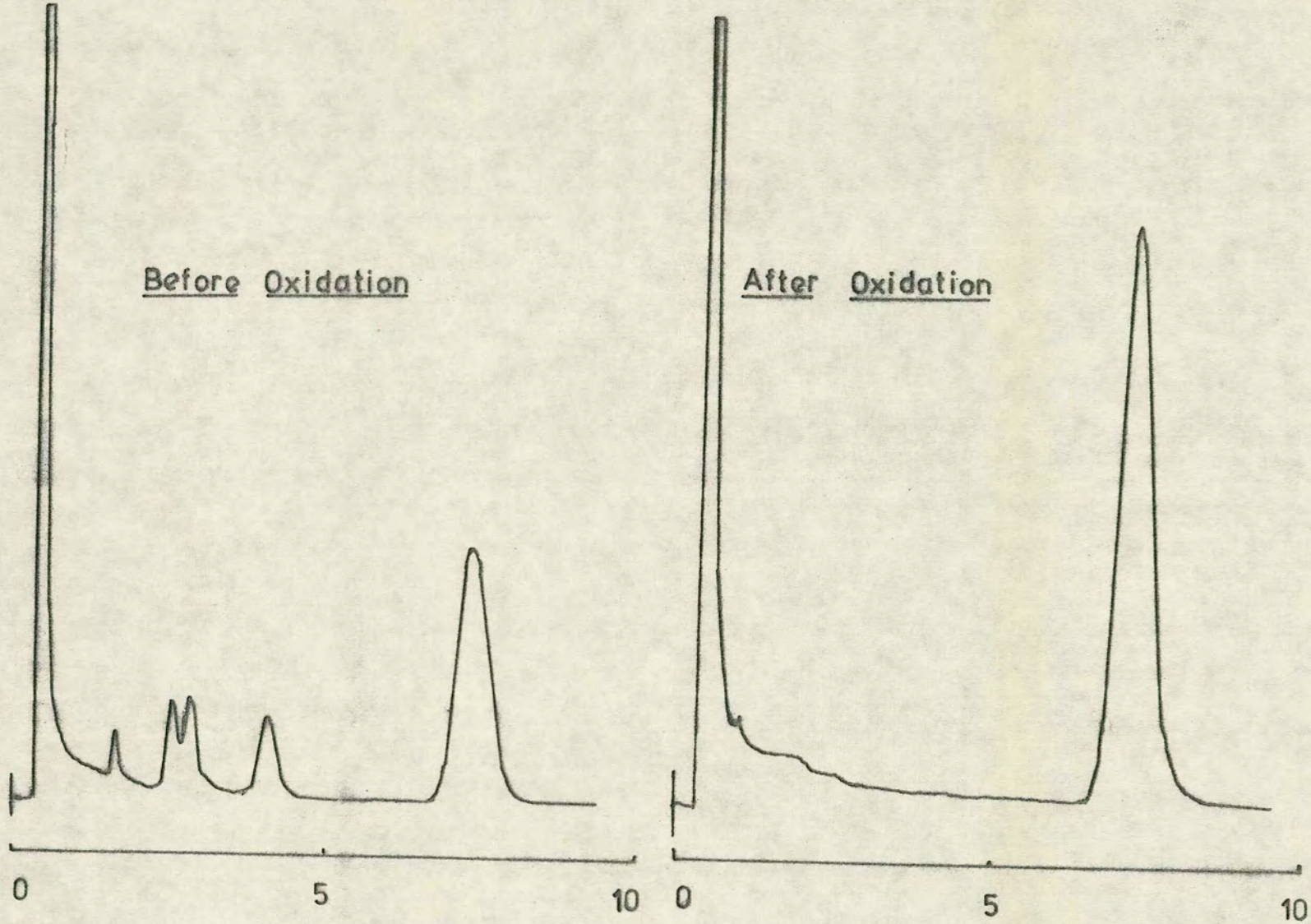


Fig. (xxxvii)

This then reacts by substitution into the aromatic ring substituent to give (12)/(14) as the major hydrocarbon product. The small proportion of the diene (41) however, must be formed *via* a singlet carbene, involving a 1,2-hydrogen shift. The singlet intermediate could arise by direct photolysis even in the presence of triplet sensitiser, or by a singlet $\rightleftharpoons$ triplet equilibrium as exists, for example, for diphenylcarbene.[124]

The reaction mixture obtained on direct photolysis through pyrex was analysed by glc (1% SE30, 175°) before hydrogenation. This showed four peaks, but furthermore, on standing, the last but one gradually reduced in size as the last peak increased. This meant that one of the initial products gradually reacted to give a more stable product. The reaction involved was presumably an air-induced oxidation, since dry solvents were employed throughout. A solution of the reaction mixture was therefore left open to the air for two days to effect a complete conversion of the initial unstable product to the new compound (63). GLC traces for initial and final mixtures are shown in fig. (xxxvii). Chromatographic separation of the mixture then gave 25% of hydrocarbon products (diene:cyclopentaindene = 1:6) as above, and a yield of 69% of the unknown compound (63). The latter did not undergo any change when put through the hydrogenation sequence, and was tentatively assigned structure (63) on the basis of its spectral data.

Mass/...

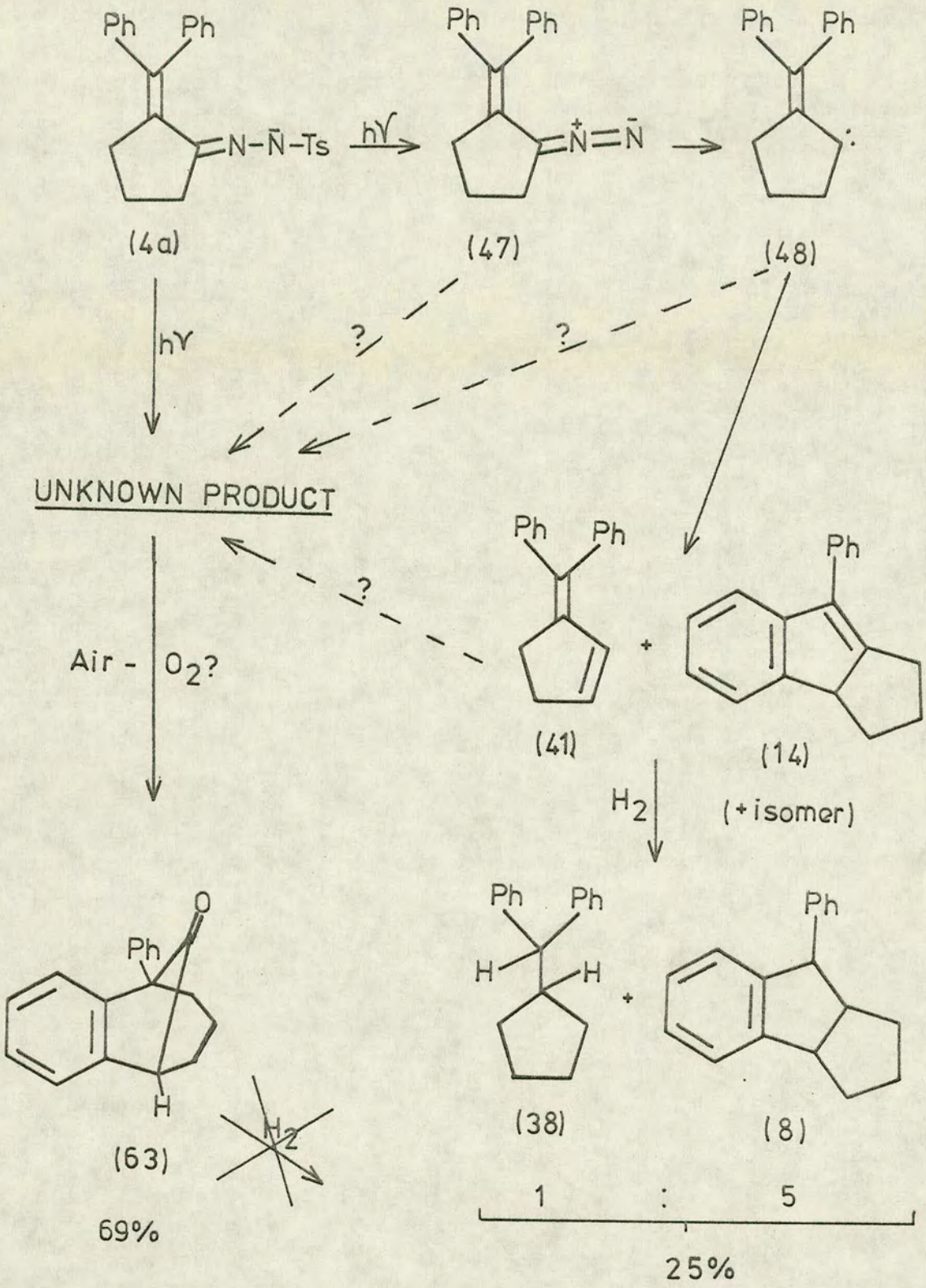
NMR Spectra of Compound (63)

Solvent	Resonance	Line Pattern	Integration
CCl_4	2.8τ	(m)	
	3.2τ	(m)	1H
	6.5τ	apparent triplet	1H
	7.7τ	(m)	2H
	8.0τ	(m)	2H
	8.4τ	(m)	2H
C_6D_6	2.8τ	(s)	5H
	3.0τ	(m)	3H
	3.32τ	(m)	1H
	6.64τ	two overlapping doublets	1H
	7.86τ-8.8τ	(m)	6H

TABLE (8)

Mass measurement of the molecular ion gave the molecular formula as $C_{18}H_{16}O$, and the first two breakdown steps in the cracking pattern were two subsequent losses of 28, probably corresponding to the loss of CO and $CH_2{=}CH_2$ respectively. The infrared spectrum showed an intense band at 1750cm^{-1} suggesting a five-membered cyclic ketone. The nmr spectrum was run in both carbon tetrachloride and perdeuteriobenzene (table (8)). Due to the unusual intensities of the lines of the "triplet" at 6.5τ (CCl_4), this was suspected to be a pair of overlapping doublets. Irradiation at 8.2τ reduced the "triplet" to two lines of relative intensities of 4:1 confirming the above hypothesis. Re-running the spectrum in perdeuteriobenzene achieved resolution of this resonance into two overlapping doublets which collapsed to a singlet on irradiation at 8τ . Thus, the single proton at 6.5τ was coupled unequally to only two other hydrogen atoms. The aromatic region is consistent with a free phenyl group and an ortho-disubstituted benzene ring as shown by the perdeuteriobenzene spectrum. The aliphatic region is consistent with the presence of three different methylene groups.

These data are accommodated by structure (63) (scheme (29)) but there may be other structures which would fit equally well and hence the structural assignment is only tentative at this time. The mechanism of formation of this compound will require further investigation, and to achieve this end, the isolation and identification of/...


Ph Ph
N-N̄-Ts
hν
(4a)
(47)
(48)
?
?
UNKNOWN PRODUCT
Air - O2?
(41)
(14)
(+isomer)
H2
O
Ph
H
(63)
69%
H2
(38)
(8)
1 : 5
25%

Scheme (29)

of its precursor, the unstable proximate reaction product, are of immediate concern. However, while these problems remain, the main purpose of the photochemical experiments i.e. to demonstrate that (48) is the precursor to (41) and (12) and/or (14) while (25) is the precursor to (12) and/or (14) and (19) as suggested in scheme (26) has been achieved thus supporting the mechanistic conclusions reached for the thermal decomposition of the benzodiazepine (5a).

P U B L I C A T I O N

Thermolysis of 3*H*-1,2-Benzodiazepines

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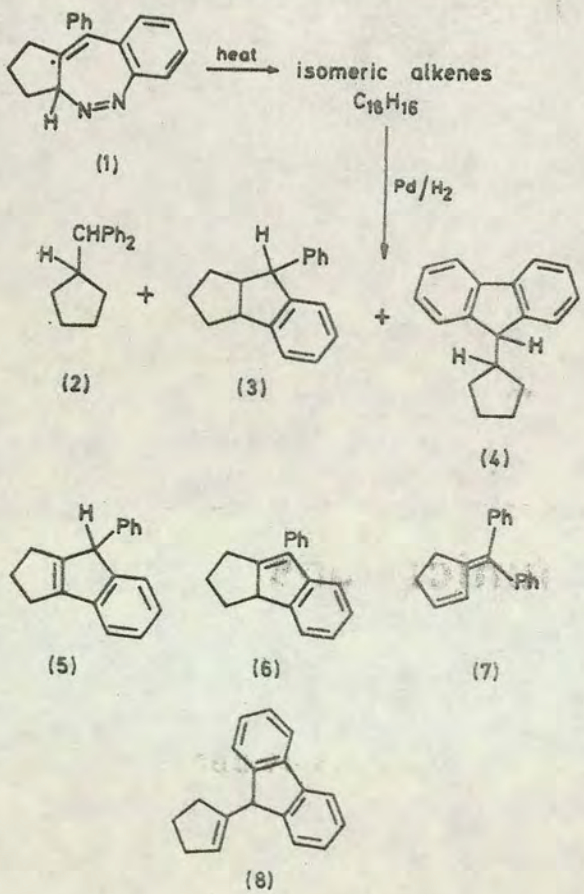
Thermolysis of 3*H*-1,2-Benzodiazepines

By R. McEWAN and J. T. SHARP*

(*Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh* EH9 3JJ)

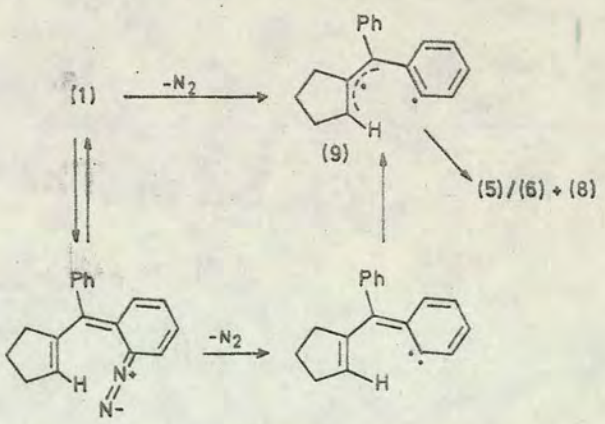
Summary The title compounds thermally eliminate nitrogen both in the gas phase and in solution but by different reaction paths involving diradical and carbene intermediates respectively.

WE have recently shown that a new group of 1,2-benzodiazepines [*e.g.* (1)] can be readily synthesised *via* the cyclisation of certain α-diarylmethylenediazoalkanes.[1] In view of the current interest[2] in the decomposition of azo-compounds it was of interest to examine the thermolysis and photolysis of these products.



Thermolysis of (1) at 400° in the gas phase and at 110—220° in various solvents generally produced mixtures of alkene isomers of molecular weight 232 which on hydrogenation gave compounds (2)—(4) which were identified by comparison with authentic samples. The alkene isomers have not yet been analysed fully; however, (7) has been isolated and the presence of (5) and (8) inferred from the n.m.r. spectra of crude pyrolysis products.

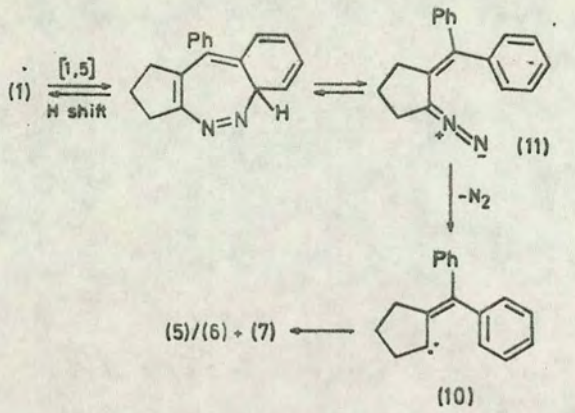
Markedly different product distributions were observed for the gas- and liquid-phase decompositions, *e.g.* in the gas phase [flash vacuum pyrolysis (f.v.p.) at 400°] the major products after hydrogenation were (3) (32%), (4) (45%), and only *ca.* 2% of (2). The very low yield of (7) as a primary product, from which (2) is derived, was confirmed from the n.m.r. spectrum of the product mixture. A control experiment showed that although (7) was partially polymerised by f.v.p. at 400° it was not converted into the other pyrolysis products. The major products can most readily be rationalised by Scheme 1 in which (1) loses nitrogen either *via* direct extrusion or *via* an electrocyclic ring opening to give the diradical intermediate (9) which undergoes coupling to give the olefinic precursors to (3), *e.g.* (6), or aromatic substitution to give (8).[3]



SCHEME 1

In the liquid-phase decomposition of (1) however, the diene (7) is a major product together with (5) and possibly (6), with (8) formed only in low yield and only in the higher-temperature reactions. For example, after hydrogenation

the products from the decomposition of (1) in boiling chlorobenzene were (2) (36%) and (3) (42%); and in boiling dodecane (2) (38%), (3) (31%), and (4) (10%). The formation of (7) and the low conversion into (8) are not readily interpreted on the basis of intermediate (9) and it is suggested that the major reaction path in the solution decomposition involves the generation of the carbene (10) (Scheme 2). There is ample precedent for hydrogen-transfer in (10) to give (7) and carbene/1,3-diradical substitutions analogous to the formation of (5) and/or (6) have recently been reported.[4] The possibility that (7) could be derived from (9) by an abstraction–disproportionation sequence with the solvent has been ruled out by decomposing (1) in perdeuteriotoluene when no incorporation of deuterium into (7) was observed. A probable mode of formation of (10) involving a sigmatropic hydrogen shift which precedes ring cleavage is shown in Scheme 2; however, its genesis *via* hydrogen-transfer in (9) is also a possibility which cannot be excluded.



SCHEME 2

The suggestion that (7) and (8) are formed from different reactive intermediates, *i.e.* (10) and (9), respectively, and that (5)/(6) are formed from both intermediates is supported by results from the photolysis of (1). After hydrogenation the products were (3) and (4) only, suggesting the intermediacy of (9), whereas the generation of (10) by the photolysis of the tosylhydrazone salt precursor to (11) gave a product which on hydrogenation contained (2) and (3) and not (4).

(*Received, 27th November* 1972; *Com.* 1976.)

[1] R. H. Findlay, J. T. Sharp, and P. B. Thorogood, *Chem. Comm.*, 1970, 909.
[2] W. P. Lay, K. Mackenzie, and J. R. Telford, *J. Chem. Soc.* (*C*), 1971, 3199, and references cited therein; R. C. Newman, jun., and E. W. Ertley, *Tetrahedron Letters*, 1972, 1225; W. D. Crow, A. R. Lea, and M. N. Paddon-Row, *ibid.*, pp. 2235 and 3207.
[3] G. Baum, R. Bernard, and H. Schecter, *J. Amer. Chem. Soc.*, 1967, 89, 5307.
[4] M. E. Hendrick, W. J. Baron, and M. Jones, jun., *J. Amer. Chem. Soc.*, 1971, 93, 1554.

PART II

OXIDATION REACTIONS OF SOME UNSATURATED, SUBSTITUTED KETONE HYDRAZONES

PAGE NO.

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II. OXIDATIONS WITH LEAD TETRAACETATE 203

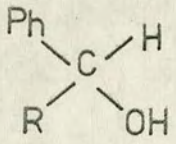
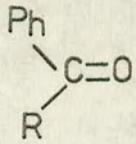
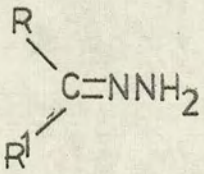
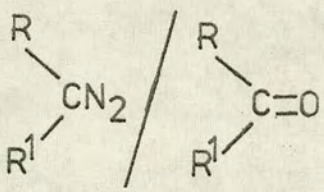
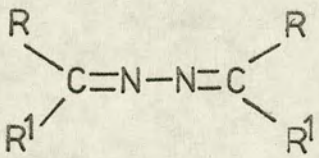
Compound Oxidised	Product	Reference
		128
$ArNH_2$	$ArN{=}NAr$	129b
R_3N	R_2NCHO / R_2NH	129a
$ArNR_2$	$ArN(R)CHO$ / $ArNHR$	129a
$ArCH_2Ar^1$	$ArAr^1CHCHArAr^1$	130
$RNHNH_2$	R-Ph (benzene solvent)	131
		132
		

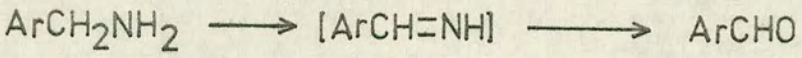
Table (A)

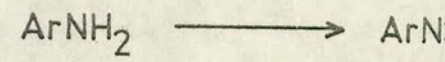
INTRODUCTION

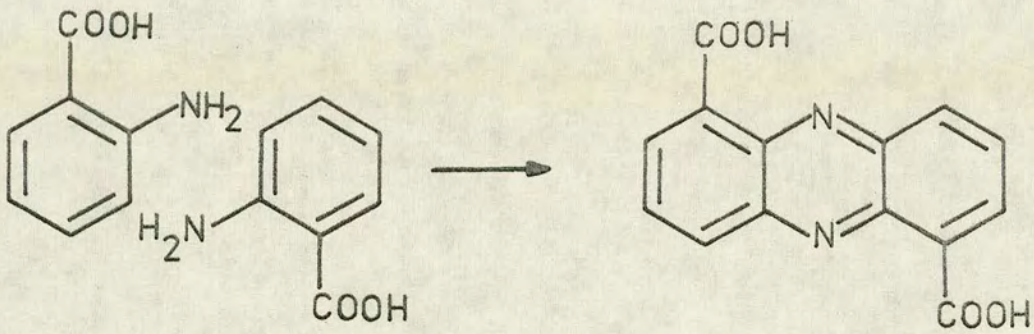
I OXIDATIONS WITH ACTIVATED MANGANESE DIOXIDE

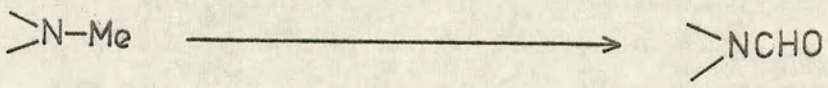
The use of manganese dioxide in an inert solvent to accomplish selective oxidation of organic compounds was first reported by Ball, Goodwin and Morton[126] in 1948. Early applications were in the field of natural products where it was shown that α,β-unsaturated alcohols were converted into the corresponding unsaturated carbonyl compounds.[127] Since these early reports, much work has been done on the oxidation of compounds as diverse as alcohols,[128] amines,[129] hydrocarbons,[130] hydrazines,[131] hydrazones,[132] oximes,[133] azines[134] etc. Some examples of these reaction types are shown in table (A).

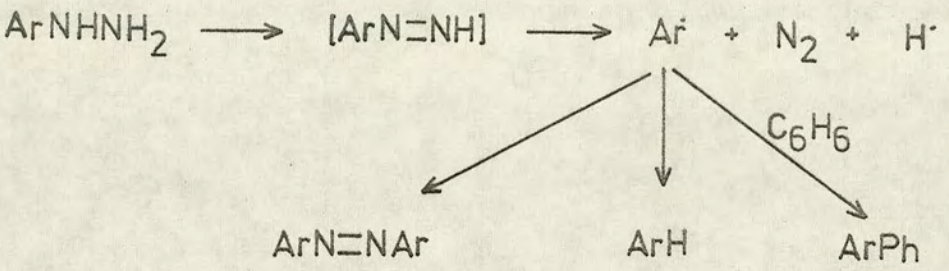
The oxidation mechanism is believed to involve free radicals which are modified in their behaviour by the fact that the reactions take place on the surface of the oxidant. Most of the kinetic investigations involving MnO_2 oxidations indicate a homolytic pathway. For example, the oxidation of benzyl alcohols,[135] hydrocarbons[130] and amines[129] have all been explained rationally by radical processes. Attempts to correlate the oxidising capacity of a particular catalyst with the type of oxide lattice and surface composition,[136] and with "available oxygen content",[137] have been made, but are not entirely conclusive.

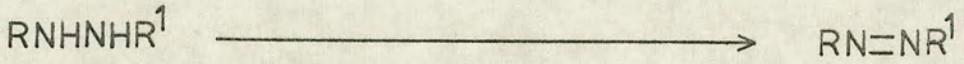






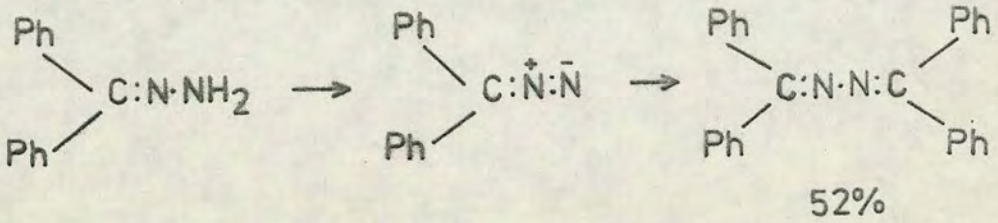






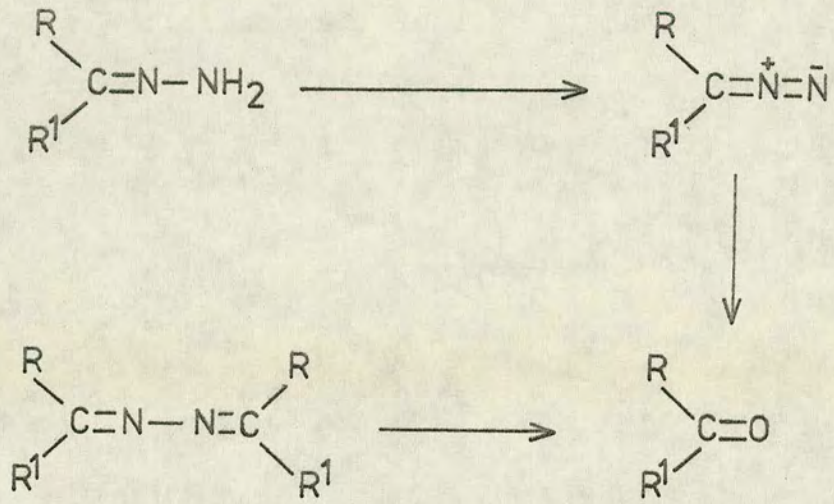
Manganese dioxide oxidations of nitrogenous compounds were first carried out on alkaloids,[138] utilising the specific capacity of this reagent for allylic oxidation as a means of structural proof. It was found, however, that the amino function, too, became involved in the oxidation process which prompted further investigations into the action of MnO_2 on simple amines,[139] hydrazine[131] and hydrazo-compounds[140] among others. Some examples of the types of reaction undergone are shown opposite.

The oxidation of hydrazones has been studied by several groups of workers. Barakat[141] reported in 1956 that oxidation of benzophenone hydrazone led to the corresponding azine by way of a diazomethane intermediate.

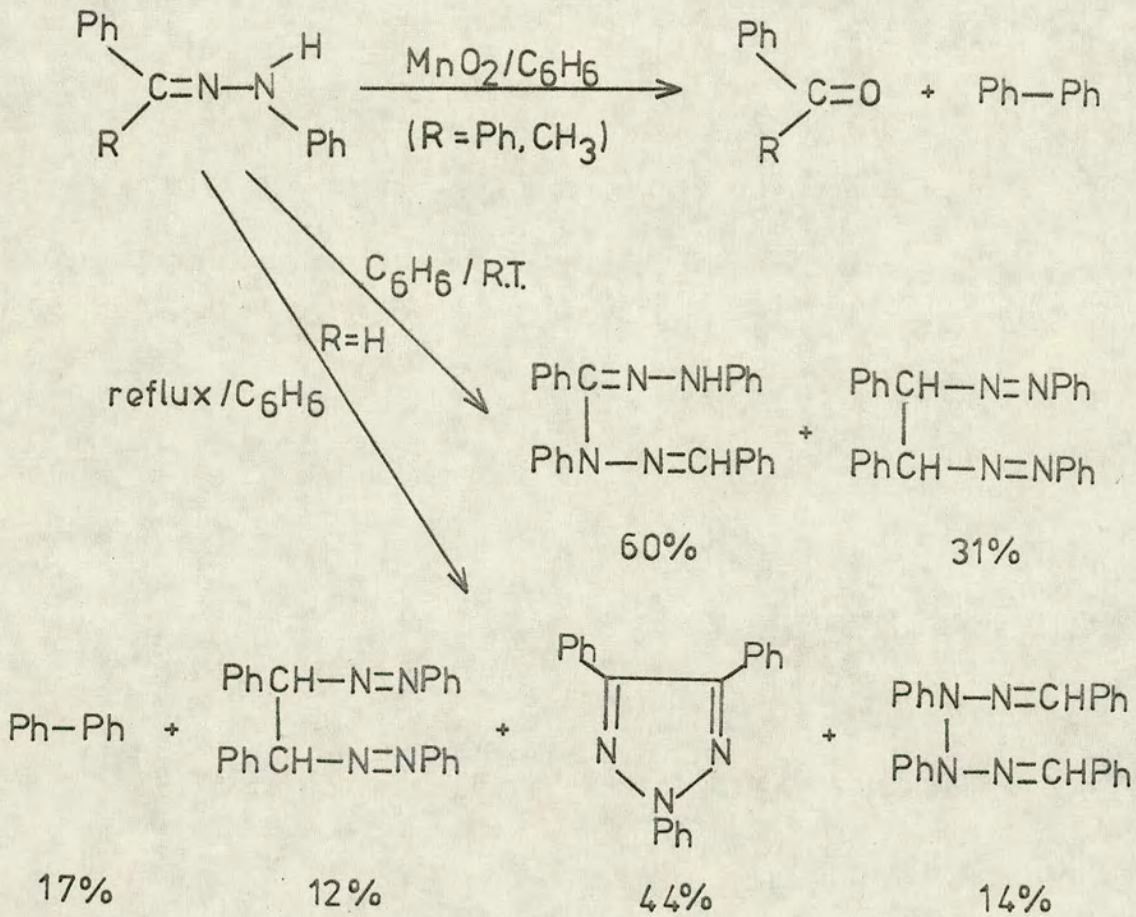


Fluorenone hydrazone reacted in a similar manner.

In the same year, Schroeder[142] patented a process for the preparation of halosubstituted diphenyldiazomethanes based on this method. There are many examples of α-ketohydrazones being converted to the corresponding diazocompounds in high yield by MnO_2, and these amply illustrate[143]/...

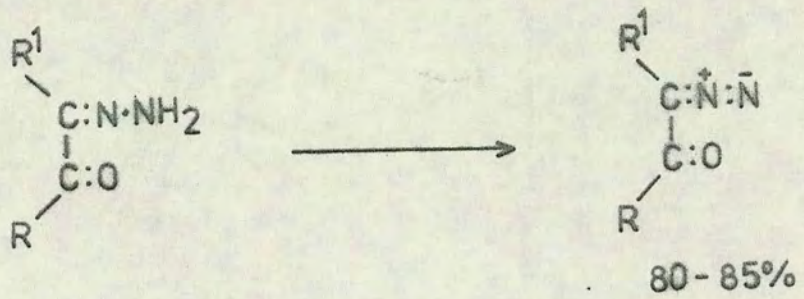


Scheme (1)



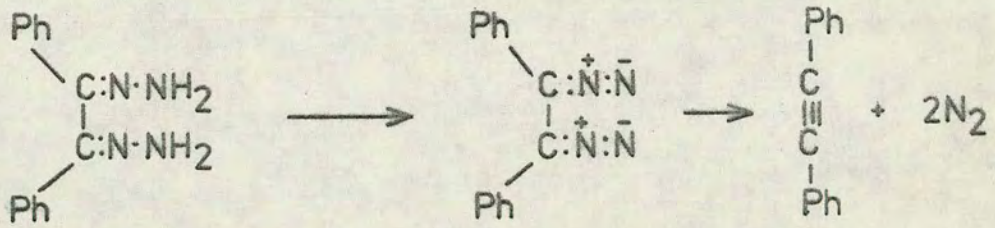
Scheme (2)

illustrate[143] the usefulness of the reagent:



R,R^1 = H, Alkyl or Aryl

However, the corresponding bis-hydrazones[143] are oxidised with loss of nitrogen:



Maier and Heep[134] have shown that many hydrazones and azines give quantitative yields of the parent ketone or aldehyde on oxidation with MnO_2 (scheme (1)). Hydrazones were shown to oxidise rapidly by way of the diazocompound while azines took from 2h to 14 days for complete reaction to occur.

The oxidation of ketone phenylhydrazones in benzene has been reported to give the parent ketone and biphenyl while/...

while aldehyde phenylhydrazones give mixtures of dimers, triazoles and biphenyl (scheme (2)).[144]

II. OXIDATIONS WITH LEAD TETRAACETATE

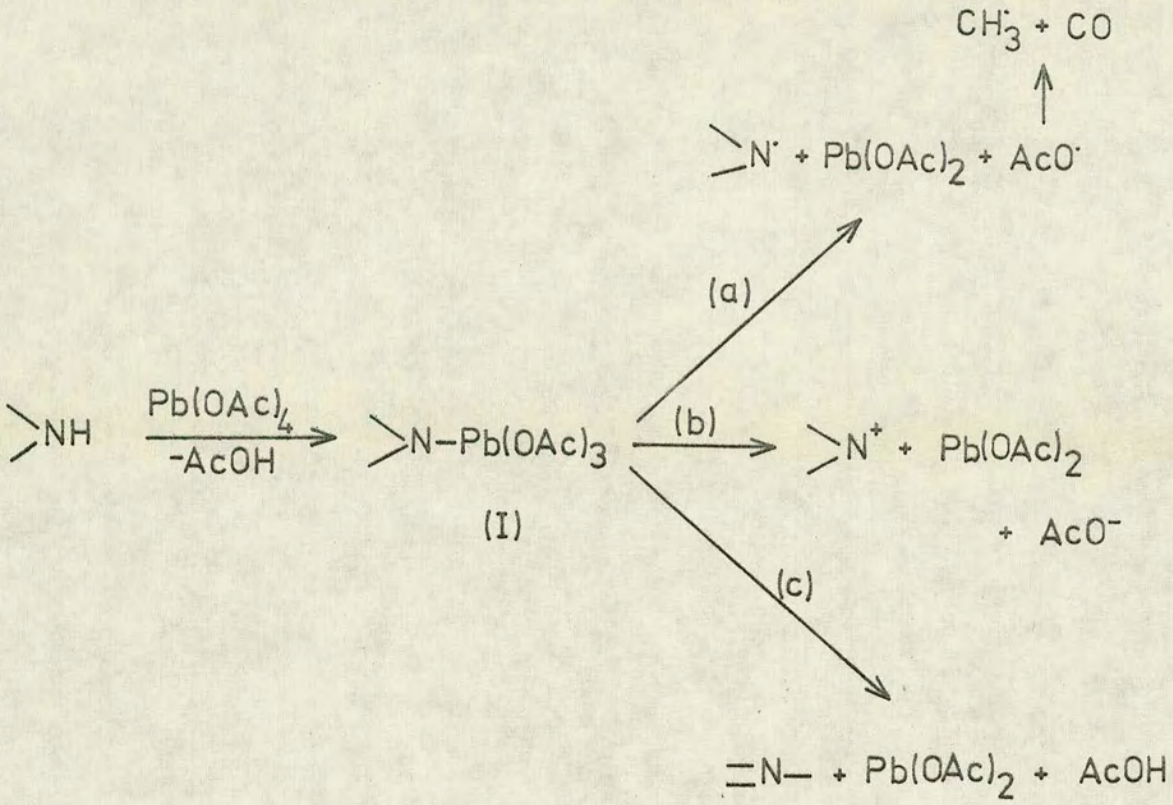
Lead tetraacetate (LTA) has been used as an oxidant in organic chemistry for almost fifty years. It is a very versatile reagent, and reviews of its reactions with 1,2-glycols,[141] sugars,[146] sterols[147] and hydrazones[148] as well as some general reviews[145] have been published.[149] The general uses of LTA in organic chemistry have recently been reviewed by Aylward.[150]

With many organic nitrogen compounds, the first step of the reaction is postulated to be the formation[150] of the N-lead triacetate complex (I) (scheme (3)). The complex (I) may be formed either by nucleophilic displacement of an acetate ligand, or, more likely by attack of a lead triacetate cation from the equilibrium:

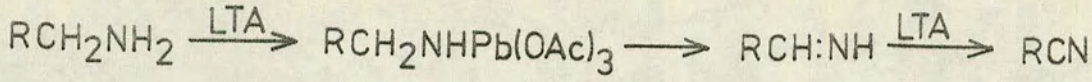
$$Pb(OAc)_4 \rightleftharpoons \overset{+}{P}b(OAc)_3 + AcO^-$$

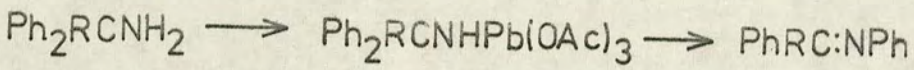
on nitrogen.

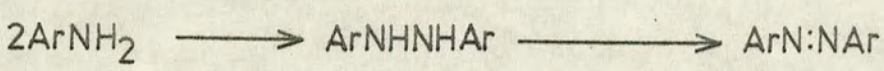
The decomposition of (I) to yield products or reactive intermediates can be heterolytic or homolytic, depending on solvent polarity, but in many cases no distinction has been made between either mechanism. Three possible pathways/...

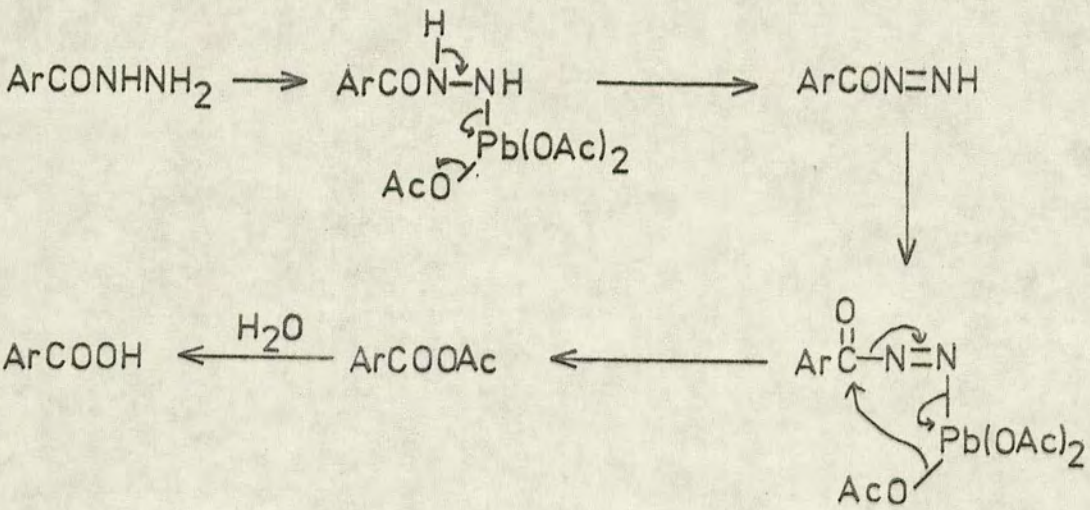

CH3 + CO
>N· + Pb(OAc)2 + AcO·
(a)
>NH
Pb(OAc)4
-AcOH
>N–Pb(OAc)3
(I)
(b)
>N+ + Pb(OAc)2
+ AcO−
(c)
=N– + Pb(OAc)2 + AcOH

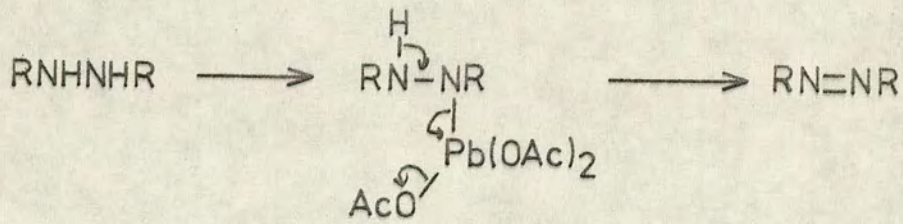
Scheme (3)


RCH2NH2
LTA
RCH2NHPb(OAc)3
RCH:NH
LTA
RCN


Ph2RCNH2
Ph2RCNHPb(OAc)3
PhRC:NPh


2ArNH2
ArNHNHAr
ArN:NAr


ArCONHNH2
ArCONNH
Pb(OAc)2
AcO
ArCON=NH
ArCOOH
H2O
ArCOOAc
ArC
N=N
Pb(OAc)2
AcO


RNHNHR
RNNR
Pb(OAc)2
AcO
RN=NR

pathways by which (I) can decompose are shown in scheme (3). These are:

(a) decomposition to a nitrogen radical, lead diacetate and the unstable acetoxy radical;

(b) loss of lead triacetate as the anion, or concerted loss of lead diacetate with formation of the nitrogen cation;

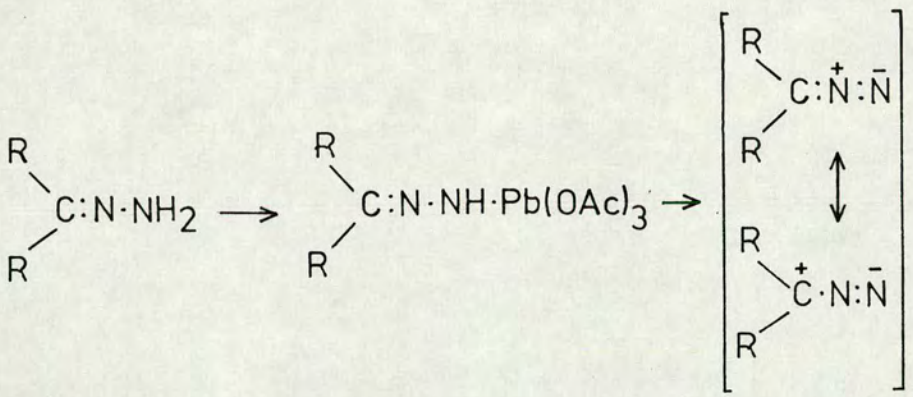
(c) loss of a proton or cationic group from an atom bonded to nitrogen: again, lead triacetate may be lost as the anion or in an overall concerted process.

A number of other pathways exist for the decomposition of (I), but unfortunately, in only a few cases has a systematic study of reaction conditions been made, and even then, a definite mechanism could not always be assigned.[150]

Although compounds of type (I) are postulated in almost all reactions with organic nitrogen compounds in no case has such a complex been isolated.

A large number of organic nitrogen compounds have been oxidised by LTA, but a comprehensive review will not be presented here. The products of oxidation of compounds containing the amino group are determined largely by whether it is attached to an alkyl or aryl residue,[151-154] some typical examples being shown opposite along with some oxidations of hydrazines.[155-157]

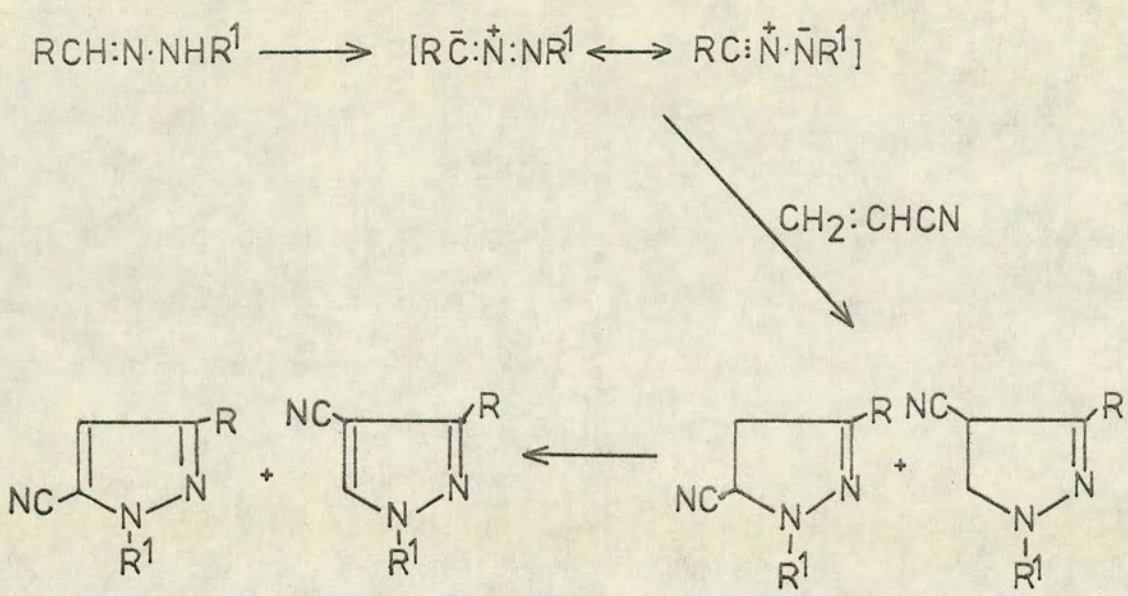
N-Unsubstituted hydrazones are dehydrogenated to the corresponding diazocompounds on reaction with LTA. Again, a lead triacetate complex has been postulated as an intermediate.[158] This decomposes under the reaction conditions to give a diazocompound which may be the isolated product:[159-161]



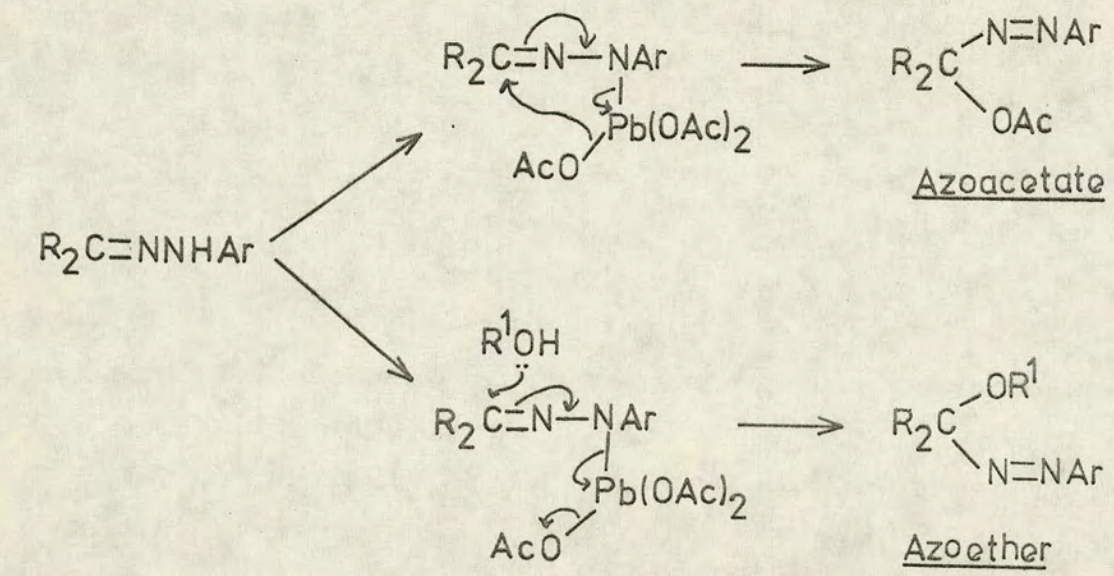
R = CF_3, CN, Ph

The more usual reaction[158] is attack by a further molecule of LTA to give rise to a diacetoxy derivative, or by acetic acid to give an acetoxyalkane.

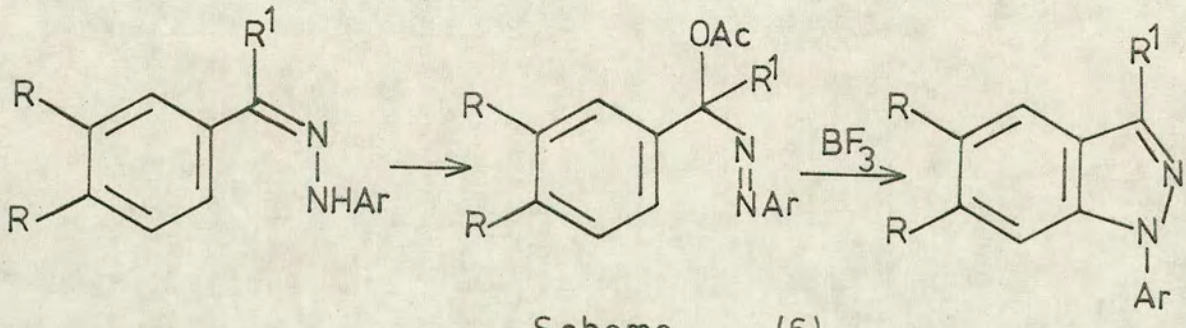
Norman and Gladstone[162,163] have recently developed a convenient method for the preparation of nitrilimines involving/...



Scheme (4)



Scheme (5)



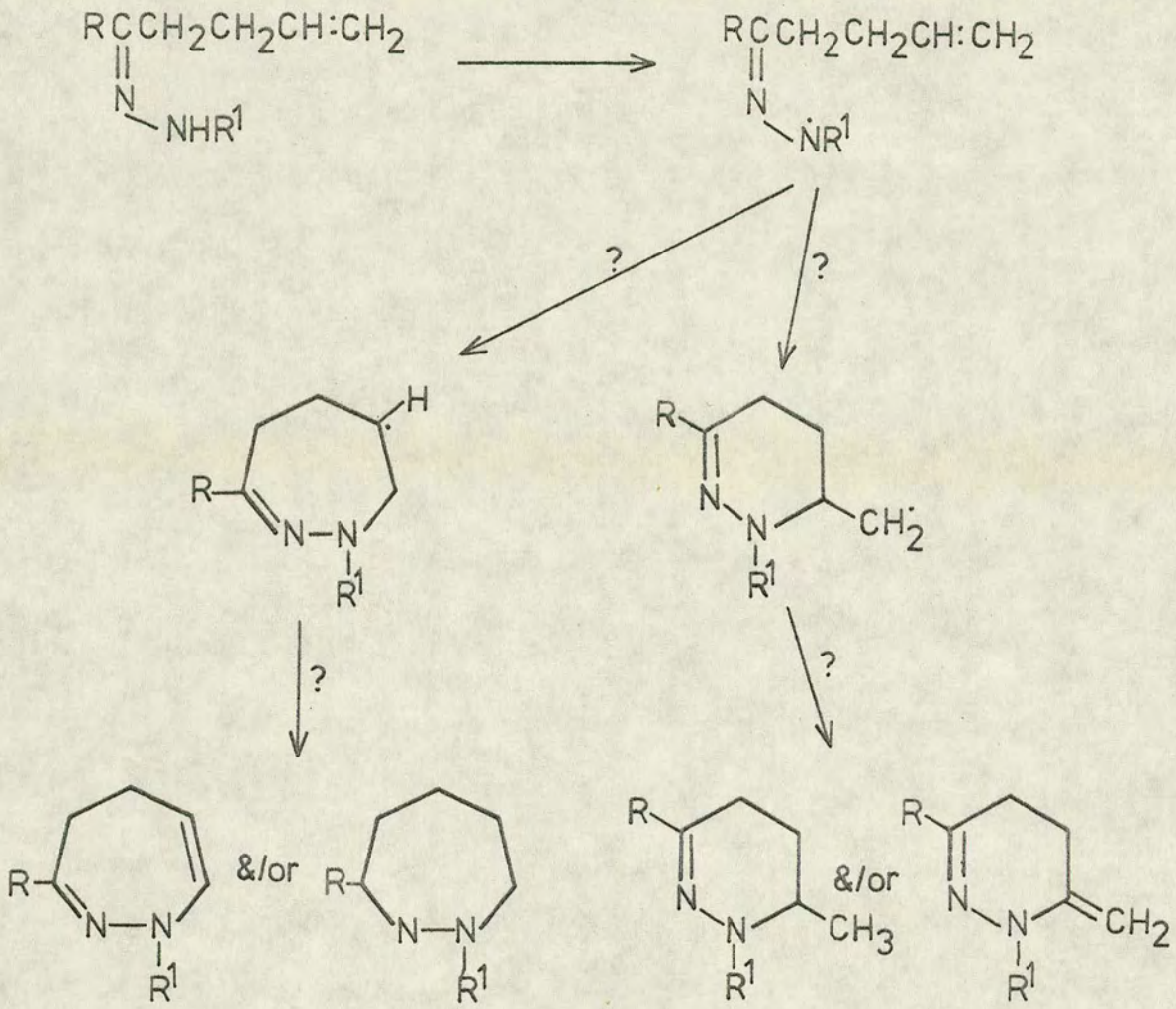
Scheme (6)

involving the LTA oxidation of aldehyde N-substituted hydrazones. For example, arylnitrilimines produced in this way can be trapped as pyrazolines, or more generally as the further oxidised pyrazoles when reaction is carried out in acrylonitrile (scheme (4)).

The same workers have also shown that hydrazones with appropriately located substituents may be oxidatively cyclised with LTA *via* nitrilimines, to form various heterocyclic compounds:

The hydrazones of ketones, however, react in a completely different manner, usually to azoacetates[164]. These compounds are formed by an intramolecular mechanism, (scheme (5)), but in alcohol solution the lead triacetate complex is intercepted to form an azoether.[165,166]

The azoacetates are themselves useful intermediates, as, on treatment with boron trifluoride and other Lewis acids, they readily lose acetate and cyclise[166]. Thus, 1-aryl-indazoles, 3-substituted-1-arylindazoles, pyridylindazoles and thiophenylindazoles have been synthesised by this method[165,166] (scheme (6)). Oxidative cyclisation of ketohydrazones/...



$R, R^1 = CH_3, Ph$

Scheme (7)

ketohydrazones can occur when there is a nucleophilic function in the ketone residue capable of displacing the lead salt from the lead triacetate intermediate.[167] Amide, alcohol and carboxyl functions are nucleophilic enough to bring about this cyclisation, while it has been suggested that olefinic and ethoxycarbonyl groups are not.[167] Pyrazoles have been reported[166] to be formed from α,β-unsaturated hydrazones of type (A) on oxidation with LTA:

$$RCH{:}CH{\cdot}CPh{:}N{\cdot}NHPh$$

(A)

In view of the possibility of obtaining cyclic products from unsaturated hydrazones, it was decided to investigate the oxidation of allylacetone and 4-pentenophenone phenyl-hydrazones and methylhydrazones in an attempt to prepare seven-membered heterocyclic compounds, possibly by scheme (7).

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PREPARATION OF KETONES AND HYDRAZONES

5-Hexen-2-one (Allylacetone)[168]

To "super-dry" ethanol (600ml) was added sodium metal (36.67g, 1.43 mole) and this was allowed to dissolve completely. Ethyl acetoacetate (185.7g, 1.43 mole) was added dropwise, and the resulting solution was heated under reflux for several minutes then allowed to cool to about 50°C. Allyl bromide (173g, 1.43 mole) was added dropwise with stirring and the mixture was heated under reflux until neutral. Most of the solvent was evaporated under reduced pressure, water (250ml) added to the residue and the resulting solution was extracted with ether (3 x 100ml). The extracts were combined and washed with water (1 x 50ml). After drying, the ether was evaporated under reduced pressure to yield a yellow oil which gave two major fractions on distillation:

1) 60-70°/25mm Hg (40g)
2) 98-102°/25mm Hg (81g)

These were shown by glc (2% NPGS, 100°) to contain about 74% and 86% of ethyl-α-allylacetoacetate respectively. Ethyl α-allylacetoacetate (62.5g of the crude mixture) was added to potassium hydroxide (27.5g, 0.5 mole) in water (230ml) at 0°, and the suspension stirred at ca. 4° for three days. The small amount of oil which formed after this time was removed by extraction into petroleum ether/...

ether (10ml). Concentrated sulphuric acid (27ml) in water (45ml) was added to the alkaline solution and the mixture was heated under reflux until no more carbon dioxide was given off (about 1h). The separated oil was removed and the aqueous solution extracted with petroleum ether (2 x 50ml) after saturation with brine solution. The extract was combined with the separated oil and the solution was washed with dilute alkali solution (1 x 20ml), water (1 x 20ml) and saturated sodium chloride solution (1 x 10ml). After drying, the solvent was evaporated under reduced pressure and the residue distilled to give 5-hexen-2-one (11.55g, 42.7%), bp 50-58°/110-120mm Hg (lit.,[168] bp 127-132°/760mm Hg) as a colourless oil. This was pure by glc (10% APL, 90°).

IR (liq.): 1705cm^{-1}, C = O; 985 and 905cm^{-1}, $\overset{R}{H}\!>\!C = C\!<\!\overset{H}{H}$

NMR ($CDCl_3$): See Appendix II.1

But-3-enyl Phenyl Ketone (4-Pentenophenone)[170]

Sodium (23g, 1 mole) was dissolved in "super-dry" ethanol (500ml). When cool, ethyl benzoylacetate (192g, 1 mole) was added dropwise with stirring. The resulting solution was heated under reflux for several minutes then cooled to 50°. Allyl bromide (121g, 1 mole) was/...

added dropwise with stirring and the mixture was heated under reflux until a neutral solution was obtained. The solvent was evaporated under reduced pressure, the residue taken up in water (200ml) and extracted with ether (3 x 100ml). The extracts were combined, washed with saturated sodium chloride solution (1 x 50ml) and after drying, the solvent was evaporated under reduced pressure. The residue was vacuum-distilled to give ethyl α-allyl-benzoylacetate (164.4g, 70%) as a colourless oil bp 102-112°/0.25-0.5mm Hg

The product was shown to be pure by glc (2% NPGS, 200°).

Ethyl α-allylbenzoylacetate (28g, 0.11 mole) and water (18ml) were heated in an autoclave for twelve hours at 210°. When cold, the mixture was extracted with petroleum ether (2 x 50ml). The extract was washed once with saturated sodium chloride solution (10ml). After drying, the solvent was evaporated and the residue vacuum-distilled to give 4-pentenophenone (13.5g, 70%) as a colourless oil bp 122-124°/25mm Hg (lit.,[170] bp 128-132°/20mm Hg).

IR (liquid film): 1690cm^{-1}, C=O;

NMR (CCl_4): See Appendix II.1

Allylacetone Phenylhydrazone

Allylacetone (3.00g, 0.03 mole) and phenylhydrazine (3.48g, 0.03 mole) were dissolved in degassed ethanol (30ml) and the solution was heated under reflux under an atmosphere of oxygen-free nitrogen for one hour. The solvent was evaporated under reduced pressure and the residue vacuum-distilled to afford allylacetone phenylhydrazone (5.1g, 87%) as a yellow oil bp 120-121°/1.3mm Hg.

Found: C 76.7% H 8.3% N 15.2%; $C_{12}H_{16}N_2$ requires
C 76.7% H 8.5% N 14.9%

IR (liquid film): 3340cm^{-1}, NH.

NMR: See Appendix II.2

Allylacetone Methylhydrazone

Allylacetone (2g, 0.02 mole) and methylhydrazine (1g, 0.024 mole) were dissolved in dry, degassed ethanol (30ml) and the solution heated under reflux under an atmosphere of dry, oxygen-free nitrogen for 1h. The solvent was evaporated under reduced pressure and the residue vacuum-distilled to afford allylacetone methylhydrazone (3g, 85%) as a colourless oil bp 38-40°/0.5mm Hg.

Found: C 66.9% H 11.2% N 22.6% $C_7H_{14}N_2$ requires
C 66.8% H 11.1% N 22.2%

IR (liquid film): 3240cm^{-1}, N-H

NMR: See Appendix II.3

4-Pentenophenone Phenylhydrazone

4-Pentenophenone (3.2g, 0.02 mole) and phenylhydrazine (2.42g, 0.022 mole) were dissolved in dry degassed ethanol (20ml) and the solution was heated under reflux under an atmosphere of dry, oxygen-free nitrogen for three hours. The solvent was evaporated under reduced pressure to afford a yellow oil which solidified on standing for several minutes. Recrystallisation from ethanol afforded 4-pentenophenone phenylhydrazone (2.4g, 48%) as white needles mp 62-64°.

Found: C 81.5% H 7.3% N 11.2% $C_{17}H_{18}N_2$ requires
C 81.6% H 7.2% N 11.2%

IR (Nujol): 3330cm^{-1}, NH

NMR: See Appendix II.3

4-Pentenophenone Methylhydrazone

4-Pentenophenone (2g, 0.0125 mole) and methylhydrazine (0.63g, 0.014 mole) were dissolved in dry, degassed ethanol (20ml) and the solution was heated under reflux under an atmosphere of dry oxygen-free nitrogen for four hours. The solvent was evaporated under reduced pressure and the residue vacuum-distilled to afford 4-pentenophenone methylhydrazone (1.5g, 60%) as a pale yellow oil bp 84-90°/0.2mm Hg.

Found: C 76.9% H 8.4% N 15.4% $C_{12}H_{16}N_2$ requires
C 76.6% H 8.5% N 14.9%

IR (liquid film): 3250cm^{-1}, NH

NMR: See Appendix II.3

OXIDATION REACTIONS WITH ACTIVATED MANGANESE DIOXIDE

Preparation of Activated Manganese Dioxide[171]

A solution of manganese sulphate tetrahydrate (110g) in water (150ml) and a solution of sodium hydroxide (40%, 120ml) were added simultaneously during 1h to a hot stirred solution of potassium permanganate (96g) in water (600ml), Manganese dioxide was precipitated soon after the start as a fine brown solid. Stirring was continued for a further hour and the solid was then collected by centrifugation and washed with water until the washings were colourless. The solid was dried at 100-120° and ground to a fine powder (92g). The finely ground powder was heated to 400° for 3h then cooled in a dessicator before use.

GENERAL PROCEDURE FOR MANGANESE DIOXIDE OXIDATION REACTIONS

To a solution of the ketohydrazone in dry, degassed benzene (1-4% w/v solutions), was added an excess of anhydrous magnesium sulphate and a four molar excess of dried, activated manganese dioxide. The mixture was stirred vigorously under an atmosphere of dry, oxygen-free nitrogen at room temperature in darkness for 15h. The solution was filtered through celite and the product isolated by evaporation of the solvent under reduced pressure and vacuum-distillation of the residue.

i) Allylacetone Phenylhydrazone

Allylacetone phenylhydrazone (2.0g, 0.011 mole), anhydrous magnesium sulphate (6g) and manganese dioxide (3.76, 0.043 mole) were stirred in dry benzene (200ml) for 2h when tlc (silica gel, benzene/petrol 50:50) showed a single spot product. This was worked up as described in the general method. The product was a deep yellow oil (4g, 70%) bp 110^{o}/0.001mm Hg, which was identified as dimeric structure (11a) as described in the discussion section.

Found: C 77.1% H 7.8% N 15.1% $C_{24}H_{40}N_4$ requires
C 77.1% H 8.0% N 15.0%

IR Spectrum (liquid film): See Appendix II.

NMR: See Appendix II.4

ii) Allylacetone Methylhydrazone

Allylacetone methylhydrazone (0.34g, 0.0027 mole), anhydrous magnesium sulphate (2g) and activated manganese dioxide (0.94g, 0.0108 mole) were stirred in dry benzene (50ml) for 1h as described in the general method. TLC on silica gel (benzene/ether, 50;50) showed a single spot product. The product was a pale yellow oil (0.34g, quant.) bp 110°/0.1mm Hg which was identified as a dimeric structure (11b) as described in the discussion section.

Found: C 67.0% H 10.2% N 22.6% $C_{14}H_{30}N_4$ requires
C 67.2% H 10.4% N 22.4%

IR (liquid film): See Appendix II.4

NMR: See Appendix II.4

iii) 4-Pentenophenone Phenylhydrazone

4-Pentenophenone phenylhydrazone (2.0g, 0.008 mole) anhydrous magnesium sulphate (4g) and activated manganese dioxide (3.25g, 0.032 mole) were stirred for 3h as described in the general method. Isolation of the product as described above gave a brown tar. The mixed products were heated under reflux in methanol (100ml) and dilute hydrochloric acid (50ml) for 80h. The solution was allowed to cool, rendered just alkaline with dilute alkali solution and extracted with ether (2 x 50ml). The extract was dried, filtered and the solvent evaporated under/...

under reduced pressure to afford a dark red oil, distillation of which gave 4-pentenophenone (0.73g, 57%) as a colourless oil bp 120-123°/23mm Hg. The product was shown to be pure by glc (2% NPGS, 118°).

IR (liquid film): 1690cm^{-1}, C=O

NMR: See Appendix II.1

iv) 4-Pentenophenone Methylhydrazone

4-Pentenophenone methylhydrazone (0.2g, 0.0011 mole) anhydrous magnesium sulphate (2g) and activated manganese dioxide (0.5g, 0.0048 mole) in benzene (50ml) were treated as described in the general method for 10h. The product was vacuum distilled to afford 4-pentenophenone (0.134g, 76%) as a colourless oil bp 124°/25mm Hg, pure by glc (2% NPGS, 101°).

IR (liquid film): 1690cm^{-1}, C=O

NMR: See Appendix II.1

OXIDATION REACTIONS WITH LEAD TETRAACETATE

Reagent: Technical grade lead tetraacetate (LTA) was used after rapid filtration from its protective covering of acetic acid, and suction-drying at the water-pump for several minutes.

General Procedure for LTA Oxidation Reactions

To a solution of the ketohydrazone in dry deoxygenated benzene was added an excess of anhydrous potassium carbonate and a fourfold molar excess of LTA. The mixture was stirred at room temperature in the dark, under an atmosphere of dry, oxygen-free nitrogen. Reactions were monitored by tlc (silica plates, benzene/ether). When all of the starting material had reacted, dilute potassium carbonate solution (50ml) was added and the mixture was shaken for several minutes then filtered through celite. The layers were separated and the aqueous extracted with ether (50ml). The benzene and ether fractions were combined, washed with saturated sodium chloride solution (1 x 20ml), dried over anhydrous magnesium sulphate and filtered. The solvent was evaporated under reduced pressure, and the residue was vacuum distilled to afford the product.

i) Allylacetone Phenylhydrazone

Allylacetone phenylhydrazone (0.27g, 0.0015 mole), anhydrous potassium carbonate (2g) and LTA (2.66g, 0.006 mole) were stirred in benzene (50ml) for 5h and the product isolated as described in the general method. Vacuum distillation of the oil obtained afforded 5-acetoxy-5-phenylazohex-1-ene (0.312g, 89%) as a red oil bp 92°/0.3mm Hg.

Found: C 68.3% H 7.1% N 11.1% $C_{14}H_{18}N_2O_2$ requires
C 68.3% H 7.3% N 11.4%

IR (liquid film): 1740cm^{-1}, C=O

NMR: See Appendix II.5

MS: See Appendix II.5

ii) Allylacetone Methylhydrazone

Allylacetone methylhydrazone (0.34g, 0.0027 mole) anhydrous potassium carbonate (2g) and lead tetraacetate (2.4g, 0.0054 mole) in benzene (50ml) were treated as described in the general method. Reaction time was 1h, after which tlc (silica gel, benzene/ether, 50:50) showed a single product. Vacuum-drying afforded an analytically pure sample of 5-acetoxy-5-methylazo-hex-1-ene (0.45g, 92%), as a yellow oil which was not distilled.

Found: C 58.7% H 8.4% N 15.1% $C_9H_{18}N_2O_2$ requires
C 58.7% H 8.7% N 15.2%

IR (liquid film): 1740cm^{-1}, C=O

NMR: See Appendix II.5

MS: See Appendix II.5

iii) 4-Pentenophenone Phenylhydrazone

4-Pentenophenone phenylhydrazone (0.40g, 0.0016 mole) anhydrous potassium carbonate (1g) and LTA (1.6g, 0.0035 mole) in benzene (50ml) were treated as described in the general method. Reaction time was 2.5h. TLC on silica gel (benzene/ether 50:50) showed a single spot product. Vacuum distillation of the product oil gave 1-acetoxy-1-phenyl-1-phenylazopent-5-ene (0.37g, 78%) as a colourless oil bp 121-126°/0.3mm Hg.

IR (liquid film): $1745cm^{-1}$, C=O

NMR: See Appendix II.5

Analysis: All attempts to obtain consistent analyses for the product failed.

iv) 4-Pentenophenone Methylhydrazone

4-Pentenophenone methylhydrazone (0.20g, 0.00106 mole) anhydrous potassium carbonate (1g) and LTA (1.2g, 0.0025 mole) were treated as described in the general method. Reaction time was 1h. TLC on silica gel (benzene/ether, 50:50) showed a single spot product. Vacuum-distillation of the product gave 1-acetoxy-1-phenyl-1-methylazo-pent-5-ene (0.23g, 87%) as a colourless oil bp 96-98°/0.2mm Hg.

IR (liquid film): 1750cm^{-1}, C=O

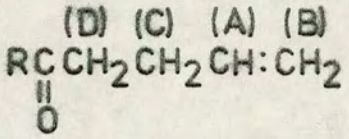
NMR: See Appendix II.5

MS: See Appendix II.5

Analysis: All attempts to obtain consistent analyses for the product failed.

APPENDIX II.I

Spectral Data of Ketones



(8)

a) R = CH_3, b) R = Ph

i) Infrared Spectra

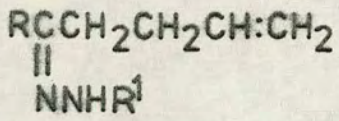
Compound	Wave number	Assignment
(8a)	1705cm^{-1}	C=O
	990cm^{-1} and 910cm^{-1}	$-CH=CH_2$
(8b)	1690cm^{-1}	C=O
	995cm^{-1} and 910cm^{-1}	$CH=CH_2$
	740cm^{-1} and 687cm^{-1}	-Ph

ii) NMR Spectra

Compound	Resonance	Line Pattern	Integration	Assignment
(8a)	(4.0-4.4τ)	m	1H	H_A
	4.9-5.2τ	m	2H	H_B
	7.4-7.9τ	m	4H	H_C, H_D
	7.9τ	s	3H	Methyl
(8b)	2.1τ	m	2H	H_o
	2.6τ	m	3H	H_m, H_q
	3.8-4.5τ	m	1H	H_A
	4.8-5.2τ	m	2H	H_B
	6.9-7.2τ	m	2H	H_D
	7.4-7.8τ	m	2H	H_C

APPENDIX II.2

Infrared Spectra of Substituted Ketohydrazones



(7)

a) R = CH_3, R^1 = Ph

b) R = CH_3, R^1 = CH_3

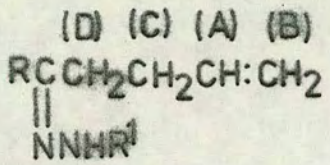
c) R = Ph, R^1 = Ph

d) R = Ph, R^1 = CH_3

Compound	Wave number	Assignment
(7a)	3340cm^{-1}	N-H
	1600cm^{-1}	C=N
	988cm^{-1} and 905cm^{-1}	-CH=CH_2
	745cm^{-1} and 690cm^{-1}	-Ph
(7b)	3240cm^{-1}	N-H
	1630cm^{-1}	C=N
	990cm^{-1} and 905cm^{-1}	-CH=CH_2
(7c)	3330cm^{-1}	N-H
	1600cm^{-1}	C=N
	983cm^{-1} and 908cm^{-1}	-CH=CH_2
	760cm^{-1}, 750cm^{-1} and 690cm^{-1}, 688cm^{-1}	two different Phenyls
(7d)	3250cm^{-1}	N-H
	1620cm^{-1}	C=N
	982cm^{-1} and 900cm^{-1}	-CH=CH_2
	752cm^{-1} and 684cm^{-1}	

APPENDIX II.3

NMR Spectra of Substituted Ketohydrazones



(7)

a) $R = CH_3$, $R^1 = Ph$

b) $R = R^1 = CH_3$

c) $R = R^1 = Ph$

d) $R = Ph$, $R^1 = CH_3$

NMR Spectrum in CCl_4

Compound	Resonance	Line Pattern	Integration	Assignment
(7a)	3.1τ	m	5H	Aromatics
	4.2τ	m	1H	H_A
	4.8-5.2τ	m	2H	H_B
	7.6-7.9τ	m	4H	H_C, H_D
	8.1τ	s	3H	Methyl
	8.45τ	s		
(7b)	3.9-4.6τ	m	1H	H_A
	4.8-5.3τ	m	2H	H_B
	5.7τ	bs	1H	N-H
	7.2τ	s	3H	$N-CH_3$
	7.8τ	m	4H	H_C, H_D
	8.2τ	s	3H	$C-CH_3$
	8.4τ	s		

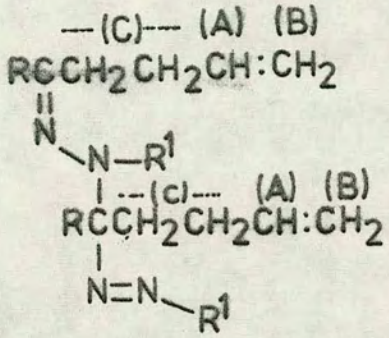
APPENDIX II.3 (continued)

NMR Spectrum in CCl_4

Compound	Resonance	Line Pattern	Integration	Assignment
(7c)	2.2τ	m	2H	Aromatics
	2.7τ	m	8H	
	3.8 -4.5τ	m	1H	H_A
	4.6-5.1τ	m	2H	H_B
	7.05-7.4τ	m	2H	H_D
	7.45-7.9τ	m	2H	H_C
(7d)	2.4τ	m	2H	H_o
	2.8τ	m	3H	H_m, H_p
	4.0-4.7τ	m	1H	H_A
	4.6-5.3τ	m	2H	H_B
	5.2τ	bs	1H	N-H
	7.0τ	s	3H	$N-CH_3$
	7.25τ	s		
	7.2-8.1τ	m	4H	H_C, H_D

APPENDIX II.4

Spectral Data for Dimeric Products Obtained in MnO_2 Oxidation



(11)

a) R = CH_3, R^1 = Ph

b) R = R^1 = CH_3

i) Infrared Spectra

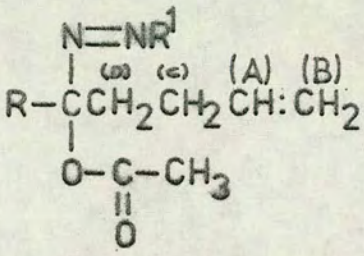
Compound	Wave number	Assignment
(11a)	1640cm^{-1}	C=N
	990cm^{-1} and 905cm^{-1}	$CH=CH_2$
	760cm^{-1} and 698cm^{-1}	-Ph
	735cm^{-1} and 687cm^{-1}	-Ph
(11b)	1638cm^{-1}	C=N
	985cm^{-1} and 900cm^{-1}	$CH=CH_2$

ii) NMR Spectra in C_6D_6

Compound	Resonance	Line Pattern	Integration	Assignment
(11a)	2.2τ	m	2H	
	2.65τ	m	2H	Aromatics
	2.9τ	m	6H	
	4.25τ	m	2H	H_A
	5.05τ	m	4H	H_B
	7.8τ	m	8H	H_C
	8.45τ	s	3H	Methyl
	8.55τ	s	3H	Methyl
(11b)	4.3τ	m	2H	H_A
	5.1τ	m	4H	H_B
	6.4τ	s	3H	$N{=}N{-}CH_3$
	7.45τ	s	3H	$=N{-}N{-}CH_3$
	8.2τ	s	3H	$N{=}C{-}CH_3$
	8.7τ	s	3H	$N{=}N{-}C{-}CH_3$
	7.0-9.0τ	m	8H	H_C

APPENDIX II.5

Spectral Data for LTA Oxidation Products



(13)

a) $R = CH_3$, $R^1 = Ph$

b) $R = R^1 = CH_3$

c) $R = R^1 = Ph$

d) $R = Ph$, $R^1 = CH_3$

i) Infrared Spectra

Compound	Wave number	Assignment
(13a)	$1740cm^{-1}$ $990cm^{-1}$ and $908cm^{-1}$ $760cm^{-1}$ and $688cm^{-1}$	C=O $-CH=CH_2$ -Ph
(13b)	$1740cm^{-1}$ $990cm^{-1}$ and $905cm^{-1}$	C=O $-CH=CH_2$
(13c)	$1745cm^{-1}$ $990cm^{-1}$ and $910cm^{-1}$ $755cm^{-1}$ and $690cm^{-1}$	C=O $-CH=CH_2$ -Ph
(13d)	$1750cm^{-1}$ $990cm^{-1}$ and $908cm^{-1}$ $755cm^{-1}$ and $700cm^{-1}$	C=O $-CH=CH_2$ -Ph

ii) NMR Spectra in CCl_4

Compound	Resonance Line	Pattern	Integration	Assignment
(13a)	2.3τ	m	2H	H_o
	2.9τ	m	3H	H_m, H_p
	4.1-4.5τ	m	1H	H_A
	4.9-5.2τ	m	2H	H_B
	7.85τ	m	4H	H_C, H_D
	8.2τ	s	3H	Methyl
	8.3τ	s	3H	Methyl
(13b)	3.9-4.6τ	m	1H	H_A
	4.8-5.3τ	m	2H	H_B
	6.25τ	s	3H	$N{=}N{-}CH_3$
	8.0τ	s	3H	$O{=}C{-}CH_3$
	8.45τ	s	3H	$\overset{N}{O}\ C{-}CH_3$
	7.8-8.8τ	m	4H	H_C, H_D
(13c)	2.4τ	m	10H	Aromatics
	2.7τ	m		
	4.1-4.5τ	m	1H	H_A
	5.0-5.3τ	m	2H	H_B
	7.4-7.7τ	m	2H	H_D
	7.9τ	s	3H	$O{=}C{-}CH_3$
	7.9-8.1τ	m	2H	H_C
(13d)	2.4-2.9τ	m	5H	Aromatics
	4.0-4.7τ	m	1H	H_A
	4.9-5.4τ	m	2H	HH_B
	6.25τ	s	3H	$N{=}N{-}CH_3$
	8.02τ	s	3H	$O{=}C{-}CH_3$
	7.0-9.0τ	m	4H	H_C, H_D

iii) Mass Spectra

Compound	m/e (% Relative Abundance)
(13a)	246(0.2), 187(3.4), 159(1.6), 141(43.6), 105(16), 99(85.7), 77(100)
(13b)	[184]*, 169(0.08), 142(4.1), 141(45.6) 125(7.3), 123(4), 100(9.3), 99(100), 98(8.7), 81(16), 71(13.2), 55(20.6)
(13d)	[246]*, 204(0.07), 160(9.4), 154(14.2), 105(100), 77(40)

* Molecular ion not observed

PAGE NO.

INDEX TO DISCUSSION

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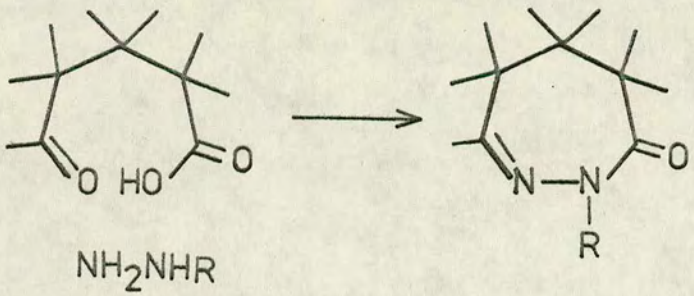
OXIDATION REACTIONS OF SOME UNSATURATED, SUBSTITUTED KETO-HYDRAZONES 234

I Preparation of Starting Materials 234

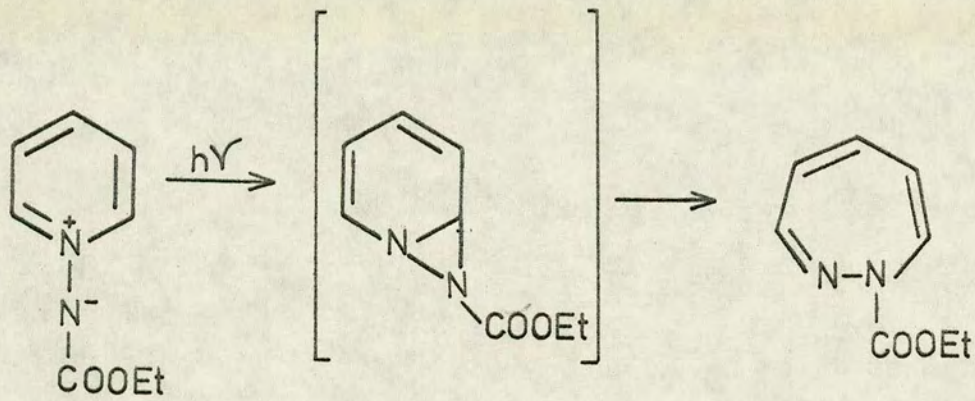
II Oxidations with Activated Manganese Dioxide 235

III Oxidations with Lead Tetraacetate 239

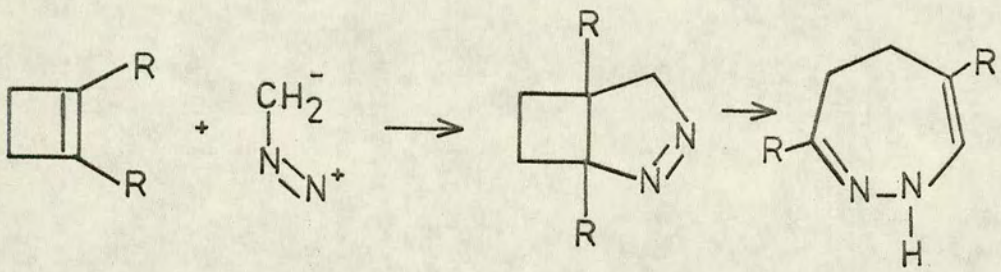
a)

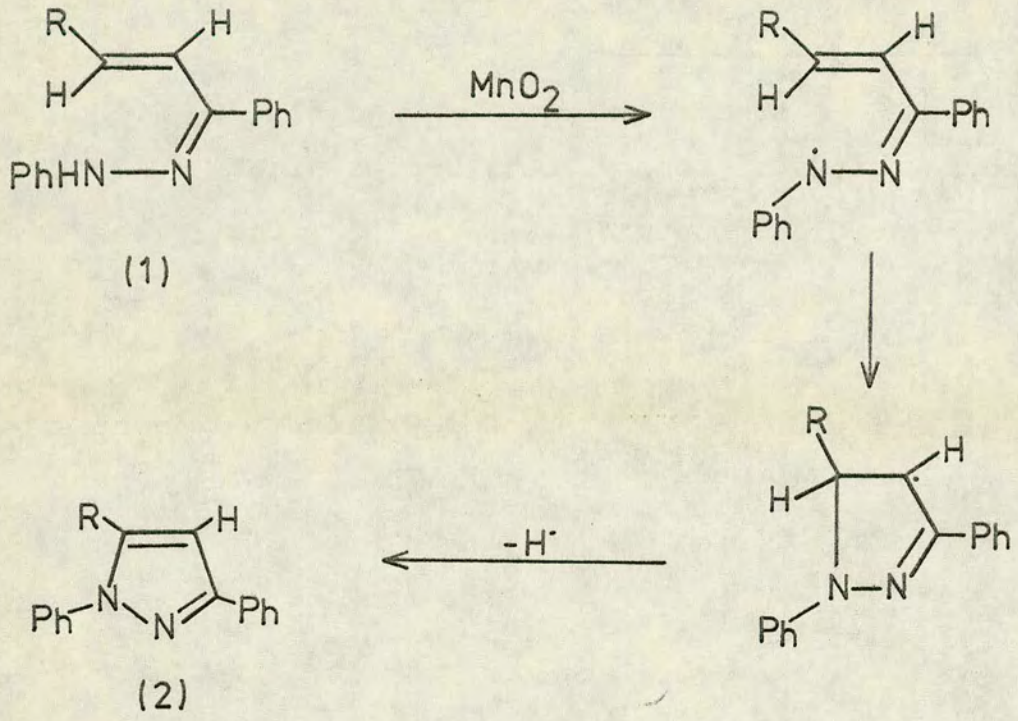

O HO O
NH2NHR
N N O
R

b)

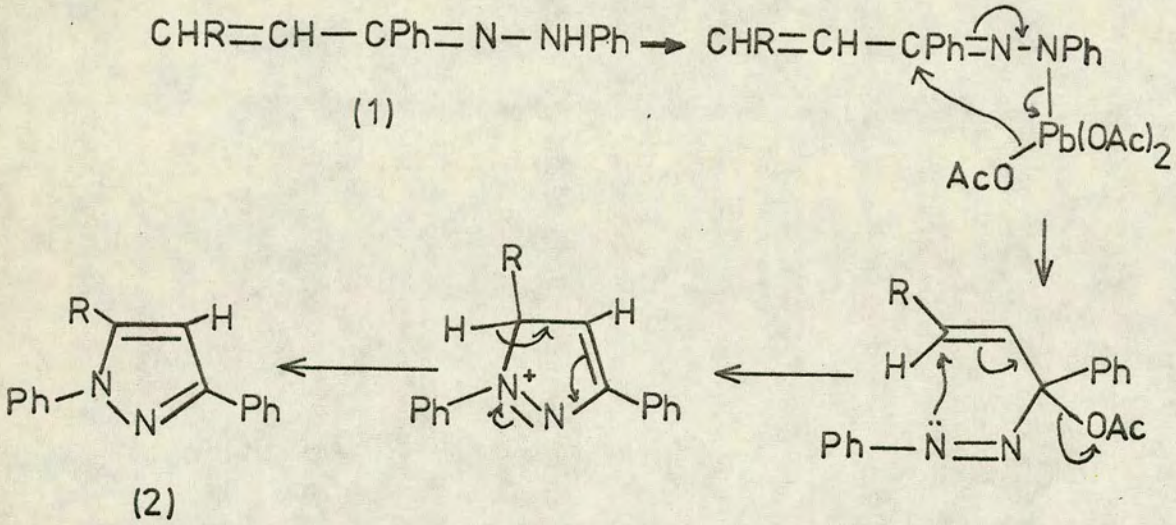

hν
N
N⁻
COOEt
N
N
COOEt
N N
COOEt

c)


R
R
CH2⁻
N
N⁺
R
N
N
R
R
R
N N
H



Scheme (1)



Scheme (2)

D I S C U S S I O N

Preamble

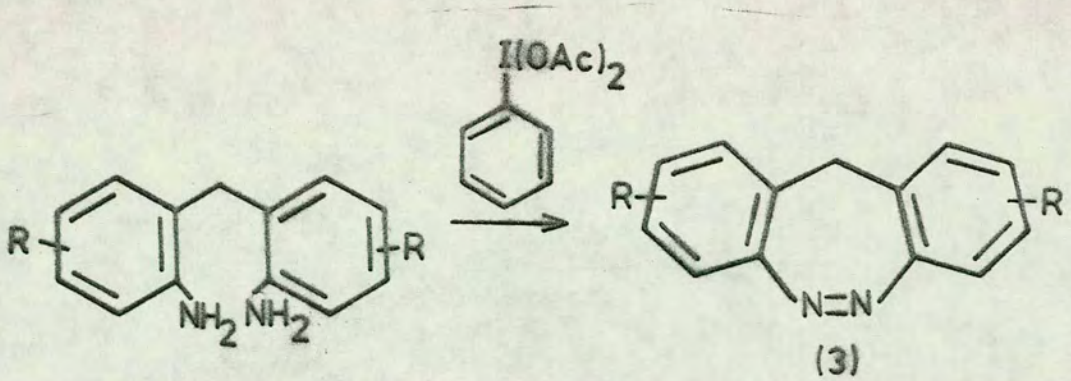
The synthesis and reactions of monocyclic 1,2-diazepines have been studied by several groups of workers.[172] The three main methods of synthesis involve:

a) condensation of an ω-dicarbonyl compd. with hydrazine,[173]

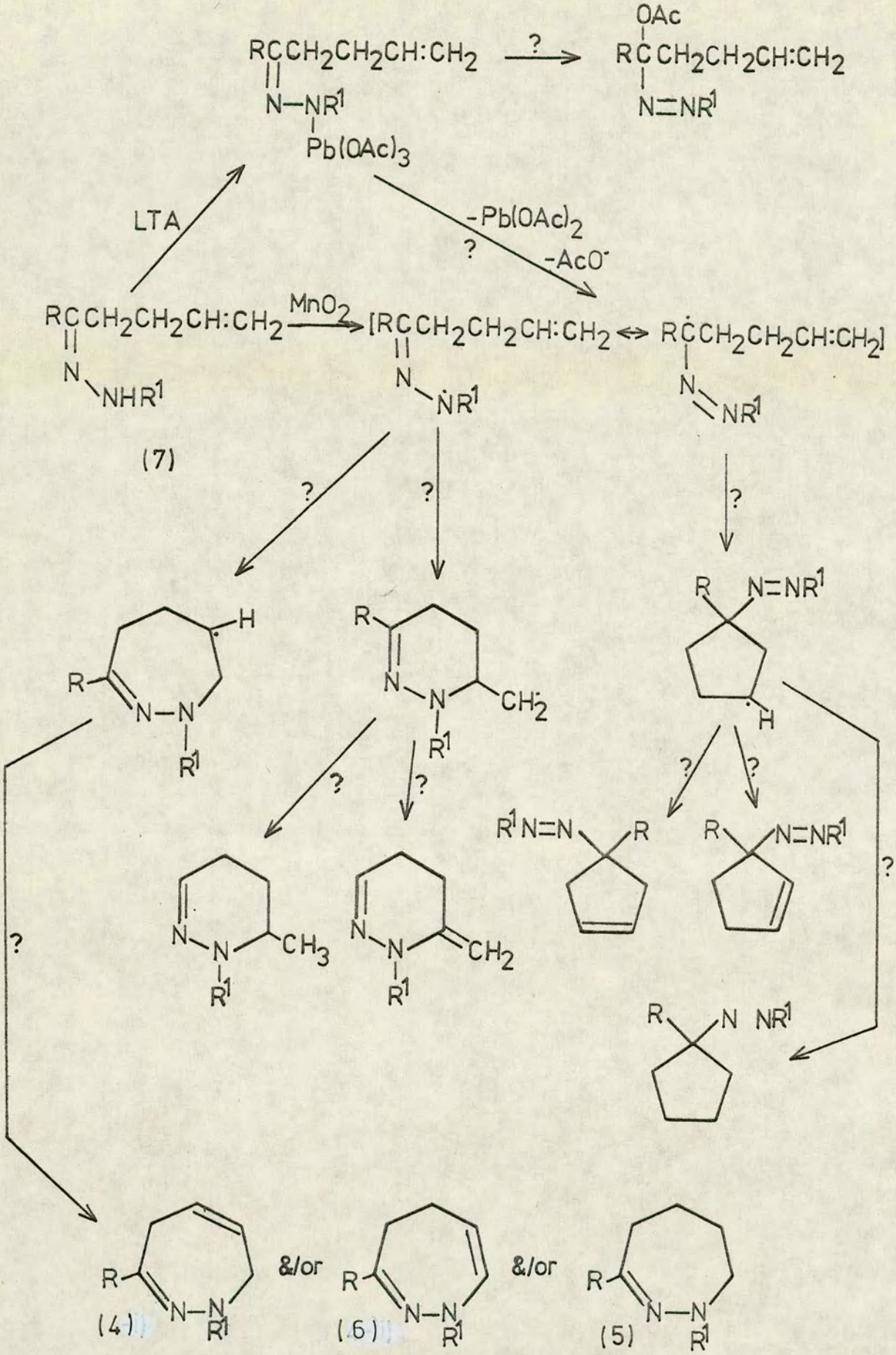
b) photolysis of a pyridinium betaine,[174]

c) reaction of cyclobutenes with diazomethane,[175] as shown opposite.

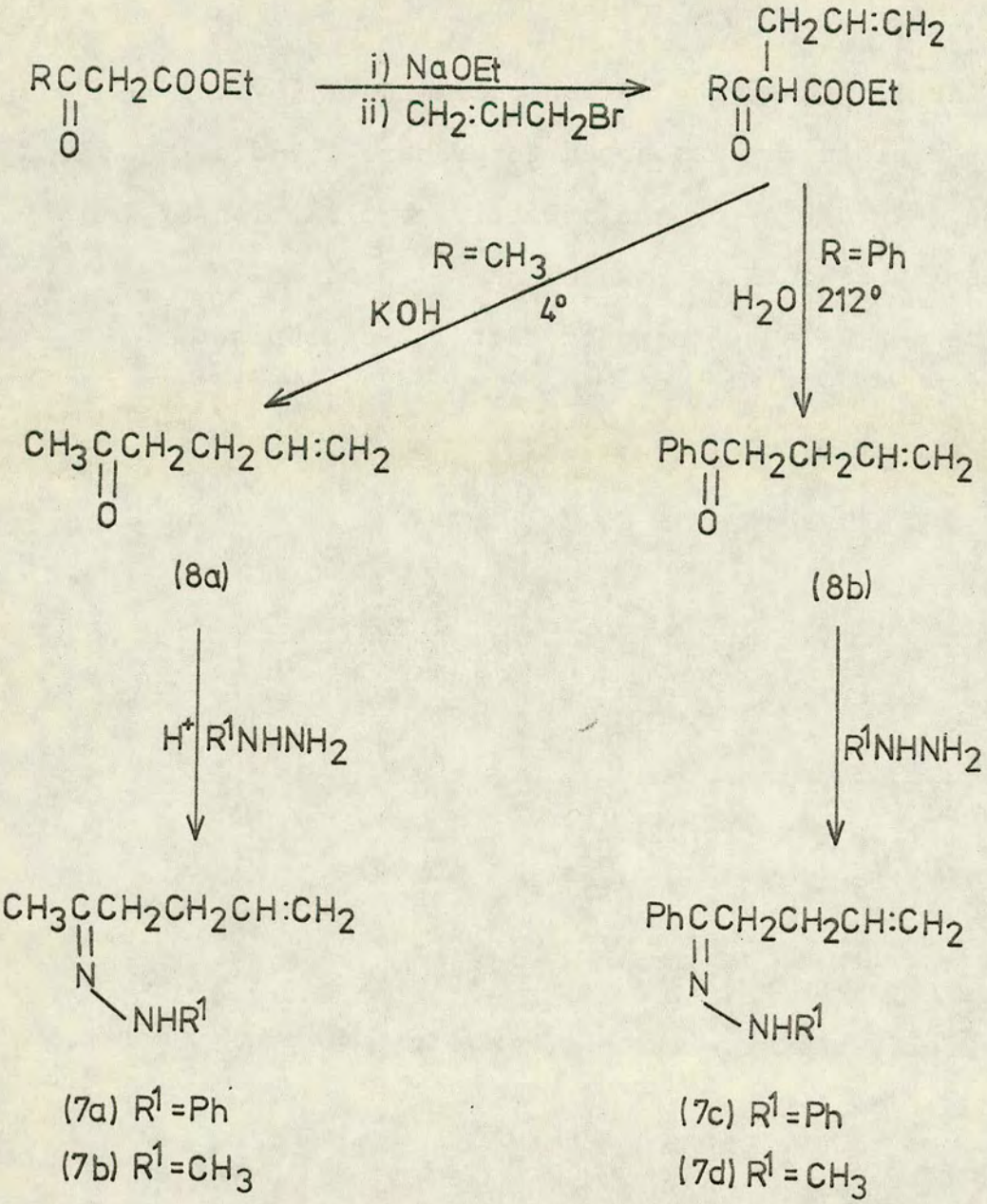
Recently, Bhatnagar and George[176] have shown that several chalcone phenylhydrazones (1) give the pyrazoles (2) on oxidation with activated manganese dioxide, and Norman and Gladstone[166] have shown that the same overall transformation occurs with lead tetraacetate (LTA), (schemes (1) and (2)). There have also been reports of the preparation of benzodiazepines of type (3) by an oxidative route:[175]



(3)


RC(=N–NR1)CH2CH2CH:CH2
Pb(OAc)3
?
OAc
RC(N=NR1)CH2CH2CH:CH2
LTA
-Pb(OAc)2
?
-AcO-
MnO2
(7)
[RC(=N–NR1)CH2CH2CH:CH2 ↔ RC(N=NR1)CH2CH2CH:CH2]
R N=NR1
H
CH2
CH3
R1N=N
&/or
&/or
(4)
(6)
(5)
R,R1 = CH3, Ph

Scheme (3)



(7a) $R^1 = Ph$

(7b) $R^1 = CH_3$

(7c) $R^1 = Ph$

(7d) $R^1 = CH_3$

Scheme (4)

By extending the length of the carbon chain in (1) by two carbon atoms therefore, it was hoped to prepare 1,2-diazepines of type (4)/(5)/(6) by the oxidative cyclisation of the hydrazones (7) as outlined in scheme (3), and to develop this as a new route to monocyclic 1,2-diazepines. As will become apparent shortly, this aim was not achieved, although some interesting reactions were observed.

OXIDATION REACTIONS OF SOME UNSATURATED, SUBSTITUTED KETO-HYDRAZONES

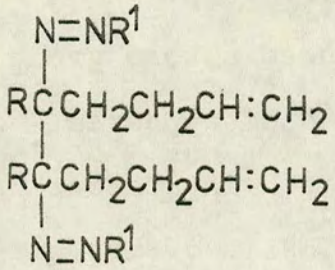
I Preparation of Starting Materials

Allylacetone (8a) and 4-pentenophenone (8b) were prepared by the base-catalysed condensation of allyl bromide with ethyl acetoacetate and ethyl benzoylacetate respectively, with subsequent hydrolysis of the product. The phenyl- and methyl-hydrazones 7(a-d) were prepared by the acid-catalysed condensation of the corresponding hydrazine with the ketone (scheme (4)). Activated manganese dioxide was prepared by precipitation from an alkaline solution of manganese sulphate and potassium permanganate.

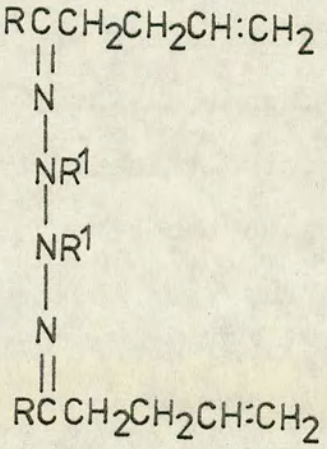
II Oxidations with Activated Manganese Dioxide

The procedure was very simple, amounting to stirring a solution of the hydrazone in dry, deoxygenated benzene with a four-molar excess of manganese dioxide for between thirty minutes and three hours. Some anhydrous magnesium sulphate was added to the reaction mixture, to remove the small amount of water which was formed. Reactions were carried out in darkness, under an atmosphere of dry nitrogen. Thin layer chromatography on silica proved to be a useful technique for monitoring reactions, since the product spots all ran ahead of the hydrazone spots when benzene/petrol was the eluting solvent.

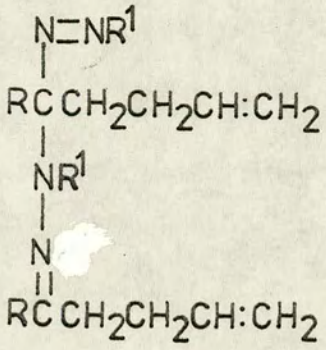
Allylacetone phenyl- and methyl-hydrazones (7a) and (7b) each gave a single product when oxidised with manganese dioxide, as was demonstrated by thin layer chromatography. It has previously been reported[144] that oxidation of ketone hydrazones led to isolation of parent ketone while oxidation of unsaturated ketone hydrazones such as chalcone phenylhydrazone, led to pyrazole-formation. Neither of these reaction-types occurred here. Instead, the products were dimeric structures for which the three possibilities are shown opposite: the C-C dimer (9), the N-N dimer (10) and the C-N crossed-dimer (11). That no cyclisation had occurred was apparent from the ir and nmr spectra of the products, which still showed the characteristics/...



(9)



(10)



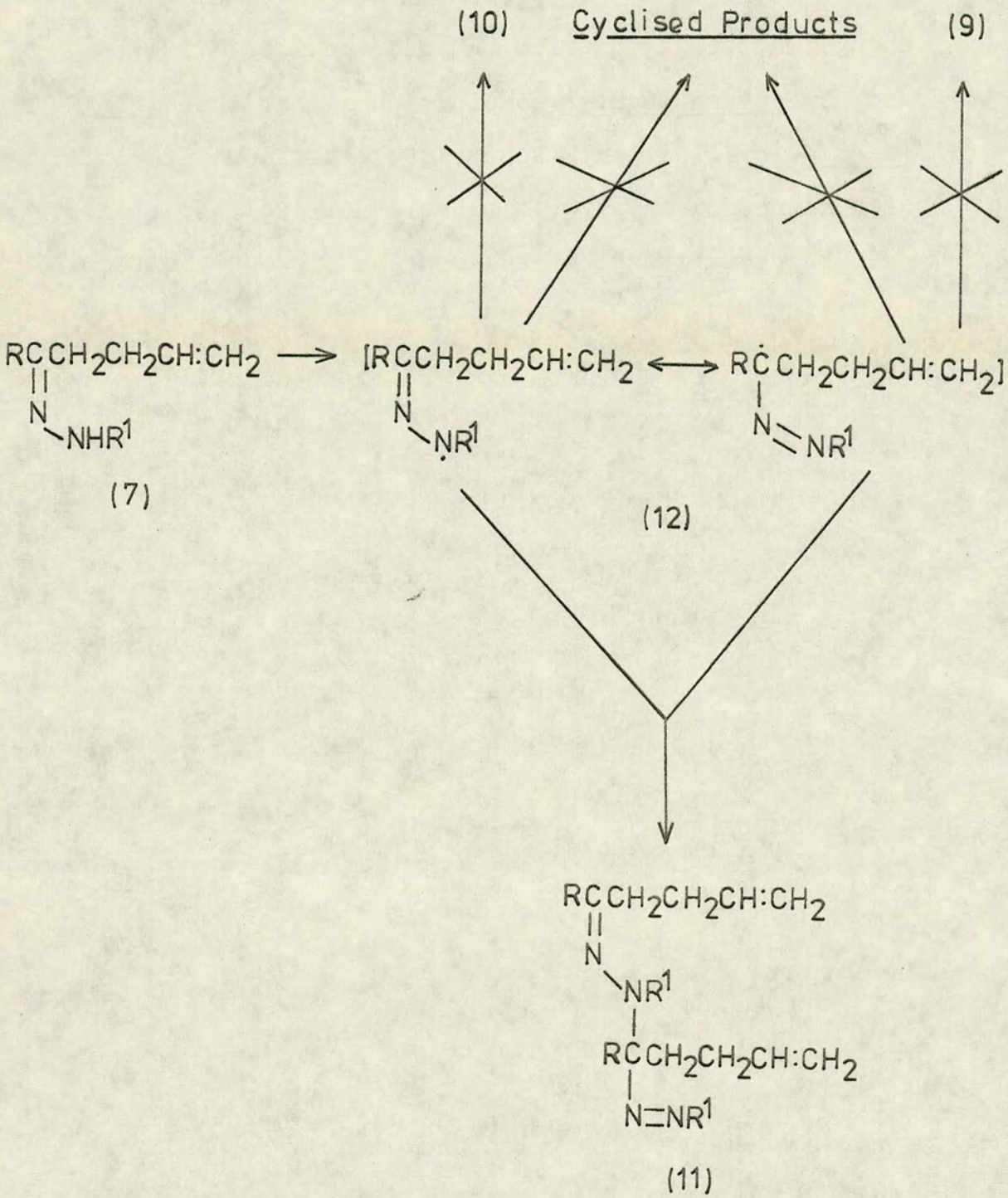
(11)

	R	R^1
a)	CH_3	Ph
b)	CH_3	CH_3
c)	Ph	Ph

characteristics of the mono-substituted alkene grouping although the -NH of the hydrazone had disappeared. The product obtained from allylacetone methylhydrazone was assigned the structure (11b) on the basis of its nmr spectrum (see Appendix II.4) which showed four different methyl resonances at 6.4τ ($N{=}N{-}CH_3$), 7.45τ ($=N{-}N{-}CH_3$), 8.2τ ($N{=}C{-}CH_3$) and 8.7τ ($N{=}N{-}C{-}CH_3$). This led to the suggestion that the product obtained from allylacetone phenylhydrazone also had a "crossed" dimeric structure (11a), and indeed, this formulation does explain the spectral data of this compound. The ir spectrum showed no N-H stretch, but the terminal olefin bands at ca. $1000cm^{-1}$ and $900cm^{-1}$ were once more in evidence. Besides these, were bands at ca. $750cm^{-1}$ and $690cm^{-1}$ characteristic of the CH bending modes of a mono-substituted benzene ring. Furthermore, there were two bands near each of these wavenumbers indicating the presence of two mono-substituted benzene rings contained in different environments. The nmr spectrum of the product gave substance to the argument. In the aromatic region, were three separated multiplets at 2.2τ, 2.65τ and 2.9τ in the ratio 2:2:6 attributable to the two aromatic o-protons adjacent to the azo-group, the two aromatic o-protons in the group Ph-N-N=C, and six other aromatic protons respectively. At 4.25τ and 5.05τ were multiplets in the ratio 2:4 consistent with two mono-substituted terminal olefin groups, and at 7.8τ was a multiplet corresponding to the methylene/...

methylene protons. Finally, at 8.45τ and 8.55τ were two singlets which could be assigned to the two methyl groups. Apparently, the effect of substituting two phenyl rings for the N-methyl groups in structure (11b) has the effect of moving the two C-methyl resonances closer together. Additional evidence for the structure (11a) was obtained from the mass spectrum which showed a highest peak of $^{m}/e$ 269 corresponding to (M-105). This is entirely consistent with a structure containing a very labile phenylazo group which is very readily lost in the mass spectrometer probe leading to the non-appearance of the molecular ion. There was no peak at $^{m}/e$ 154 (M-210) showing that the product did not contain two phenylazo groups, thus ruling out (9) as a possible structure. There was no peak at $^{m}/e$ 187 ($M/_2$) which again rules out the possibility of (9), and also (10), since symmetrical dimers are known to give large peaks at half the molecular weight by fragmentation at the central bond.

As has been reported elsewhere,[176] the oxidation of α,β-unsaturated aldehyde and ketone phenylhydrazones with MnO_2 has been postulated to proceed via radical intermediates which cyclise due to the close proximity of the terminal double bonds and the radical centres (scheme (1)). Extending the chain-length of these hydrazones by two carbon atoms such that the carbon-carbon and carbon-nitrogen double bonds are no longer conjugated/...



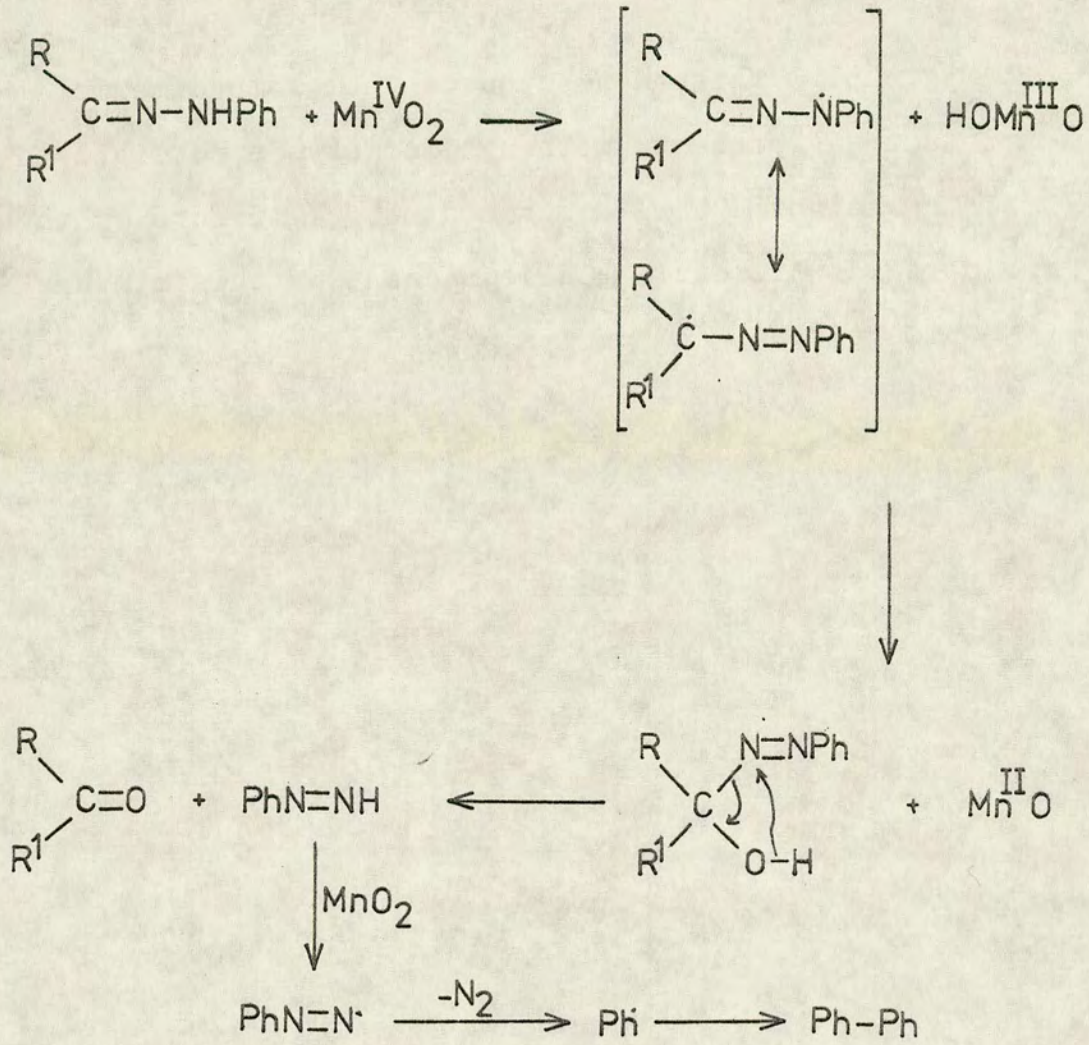
a) $R = CH_3$, $R^1 = Ph$

b) $R = R^1 = CH_3$

Scheme (5)

conjugated, seems to drive the intermediates (12) to react by intermolecular combination rather than intramolecular cyclisation, (scheme (5)), although sterically, there is no reason why (12) should not cyclise. This would suggest, then that conjugation between the terminal olefin and hydrazone moieties is a prerequisite for cyclisation, although it does not explain why the crossed-dimers (11a) and (11b) were the sole products in the oxidation of (7a) and (7b). Formation of these products must be concerned with the mechanism of adsorption of the hydrazone onto the metal oxide surface. In order to determine whether this was so, it was proposed to oxidise methyl n-butylketone phenylhydrazone in a similar manner, but no data for this is available at the present time. Thus insufficient data is available to allow a reasonable theory to be proposed as regards this reaction.

4-Pentenophenone phenyl- and methyl-hydrazones, however, reacted in a different manner, the latter being oxidised in the normal way to the parent ketone in 76% yield. This was demonstrated by nmr and ir spectroscopy of the product, and also its glc retention time (2% NPGS, 100°) which was identical with that of authentic (8b). 4-Pentenophenone phenylhydrazone however, appeared to give a mixture of products. The aromatic region of the nmr spectrum of the product showed no less than five closely-spaced multiplets, of which two were at very low field (2-2.2τ) which is suggestive of protons adjacent to an azo/...


R
C=N–NHPh
R1
+ Mn^IV O2
C=N–ṄPh
Ċ–N=NPh
+ HOMn^III O
C=O
PhN=NH
MnO2
PhN=N·
-N2
Ph·
Ph–Ph
N=NPh
C
O–H
+ Mn^II O

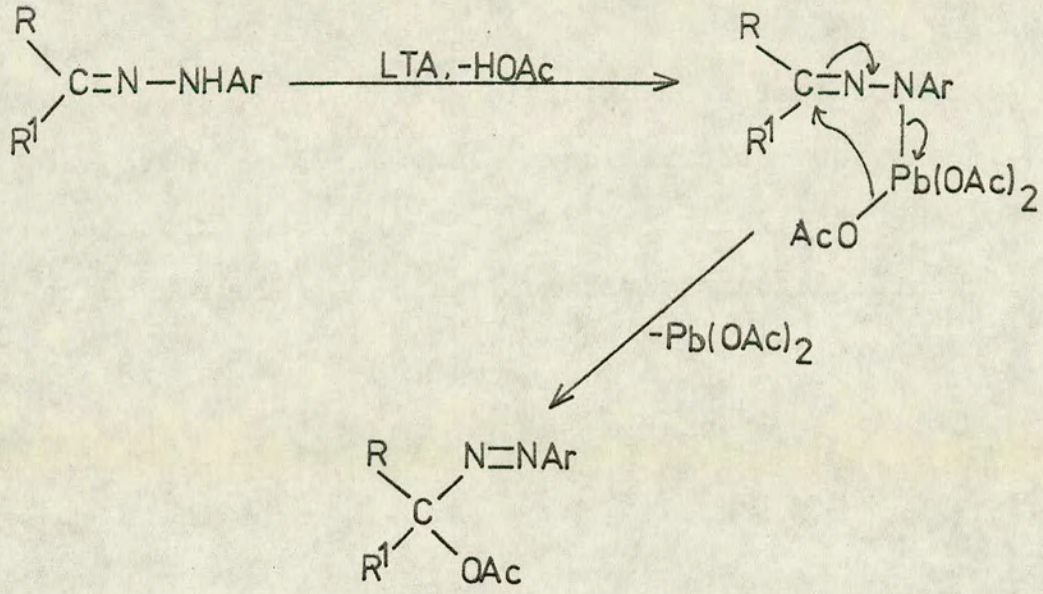
Scheme (6)

azo-group. This then suggests that some dimeric product was present, although it was not possible to state whether a single structure or a mixture of the dimers was present. One component of this mixture was identified as 4-pentenophenone (8b) by the intense absorption at 1690cm^{-1} in the ir spectrum. The mixture was not separated, but was instead hydrolysed in refluxing acid solution to afford on distillation of the product, 4-pentenophenone in 57% yield. None of the reactions described above are fully understood mechanistically at the present time, and a full-scale investigation is required to achieve this end. However, in the case of ketone formation, the source of oxygen is thought to be a hydrated form of manganese dioxide[5] such as HO-Mn^{III}=O or $(HO)_2Mn^{IV}$=O (scheme (6)).

III Oxidations with Lead Tetraacetate

Lead tetraacetate (LTA) oxidations were carried out in a similar manner to the MnO_2 reactions. The hydrazone was stirred in deoxygenated benzene with a 2-4 molar excess of LTA. Some potassium carbonate was added to the reaction mixtures to remove the small amounts of acetic acid formed. Reactions were carried out in darkness and under an atmosphere of dry nitrogen.

In accord with the observation by Norman and coworkers[178] that mono-substituted hydrazones of saturated ketones gave/...


R
C=N—NHAr
R1
LTA, -HOAc
R
C=N—NAr
R1
Pb(OAc)2
AcO
-Pb(OAc)2
R
N=NAr
C
R1
OAc

(13)

Scheme (7)

gave azoacetates on oxidation with LTA, this was the type of behaviour observed here (scheme (7). There was no tendancy to cyclise as has been observed for some unsaturated ketone hydrazones. The structures of the azoacetates (13) were fully supported by their spectral properties which are outlined in Appendix II.5.

For example, the ir spectrum of (13a) showed no absorption above 3060cm^{-1}, confirming the absence of the NH group. At 1745cm^{-1} was an intense band characteristic of an ester carbonyl group, and between 1200 and 1100cm^{-1} were a series of broad bands, again characteristic of an ester group. The mono-substituted alkene bands near 1000cm^{-1} and 900cm^{-1} showed that no cyclisation had occurred. The nmr spectrum was also consistent with the azoacetate structure. In the aromatic region were two multiplets at 2.3τ and 2.9τ in the ratio 2:3 corresponding to the two ortho-protons and the other three aromatic protons respectively. At 4.1-4.5τ and 4.9-5.2τ were two multiplets (1:2) corresponding to the terminal olefin group and at 7.85τ, a multiplet corresponding to the four methylene protons. Two singlets at 8.2τ and 8.3τ integrating for three protons each were attributed to the two methyl groups. The mass spectrum of (13a) also supported the proposed structure in showing a molecular ion of $^{m}/e$ 246 and large peaks at $^{m}/e$ 187 and $^{m}/e$ 141 corresponding to loss of the acetate and phenylazo groups respectively. Compounds 13(b-d) showed similar spectral properties

(see/...

(see Appendix II.5) and in no case was the hoped-for cyclised product obtained.

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